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ASSAY OF HEPARIN IN BLOOD: A CRITIQUE

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INTRODUCTION

AN ACCURATE method for the determination of circulating heparin would have 3 clinical uses: (1) to assess the amount of heparin in the circulating blood after therapeutic administration, (2) to check the ability of the coagulation time to reflect the heparin level, and (3) to determine the amount of heparin in the blood of a normal individual not exposed to an external or an abnormal internal source of heparin. For these reasons the various methods of heparin assay have been reviewed and one of them selected for trial.

METHODS USED

Methods of heparin assay have in the past been based either upon the anticoagulant ability of the blood containing the heparin or the ability of the heparin when separated from blood proteins to act in a coagulation system or to be measured as a mucopolysaccharide either spectrophotometrically or by the radioactivity of assimilated tagged sulfate ion.

Its anticoagulant property has been tested by recalcification clotting times[5, 7] by titration against thrombin,[13] and by titration against protamine.[1] To assay the antithromboplastic action of heparin, the addition of tissue extract to the coagulation mixture has been used by some.[7, 9, 11] Separation of the mucopolysaccharide from blood proteins has been done by the use of octylamine,[8] by phenol,[12] by heat and alkali,[2, 3] and by trypsin digestion.[4] The residue has been assayed in a coagulation system or after reaction with azure A by metachromatic methods. Eiber,[4] using tagged sulfate ion, determined the amount by radioactivity.

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There has been criticism of all the methods. With the exception of Bassiouni's second method, the metachromatic methods do not distinguish heparin from the other mucopolysaccharides, principally chondroitin sulfate, and, if the coagulation techniques are used on the material after separation from protein, the method seems to have little advantage over coagulation tests on the original specimen of blood.

Recovery.—Coagulation methods have shown excellent recoveries of heparin added to blood in vitro. McGoon[10] found 5 per cent error; Monkhouse[12] accomplished 74 to 88 per cent recovery from human whole blood. Using a metachromatic method, Bassiouni[2] showed between 85 and 100 per cent recovery, but when he separated the heparin from other acid mucopolysaccharides by precipitating the latter with methyl alcohol[3] he could recover only 50 per cent. He believed that the loss was so constant that an accurate value could be extrapolated from the data obtained. Monkhouse[12] considered the metachromatic method less accurate than that in which the test substance was titrated against thrombin when small amounts of heparin were involved, but about similar in the case of large amounts. Protamine titration methods[1, 11] have not been concerned with accurate recovery, and Allen states that the test is not an accurate method of heparin assay.

Heparin in Normal Blood.—Considerable disagreement has existed concerning the presence or absence of circulating heparin in normal blood. No method using a coagulation system without an attempt at isolation of heparin can be helpful in settling this point, since blood, the material being tested, is inevitably used as the substrate. The analytic methods mentioned have given varying results. Bassiouni found 0.3 to 2.3 mg. per 100 c.c. of normal blood using his first method,[2] but little or none by his second.[3] Freeman[6] found levels of 0.02 to 0.1 mg. per 100 c.c. Monkhouse[12] felt that there was "probably" no circulating heparin. Eiber,[4] using tagged sulfate ion, felt that 0.5 mg. per 100 c.c. was a close estimation of normal circulating heparin.

After review of the various methods, Bassiouni's second[3] was selected. After several trials it was modified in that the final step of Bassiouni which involves separation of the mucopolysaccharides from the dye by formamide was omitted. This measure was felt to be wise since the later stages of Bassiouni's method destroys a large amount of heparin. The method is then similar to Bassiouni's first,[2] possessing those valuable refinements which he added in the first part of his second.[3] We are referring principally to the addition to the analysis of heparin from the white cell layer. Other minor modifications in the constituents of the solvent, the time of centrifugation, and so forth, were made by us for greater accuracy and convenience.

Methods

I. Heparin assay

A. Reagents

1. 3.8 per cent sodium citrate
2. 0.85 per cent sodium chloride
3. 2N sodium hydroxide
4. Analytic grade ammonium sulfate
5. 1 mg. per cent azure A

6. 0.01 N hydrochloric acid
7. Standard heparin (The Upjohn Company—sodium salt)
8. Buffered solvent:
   a. 1 part N NaOH
   b. 1 part distilled H_2O
   c. 1 part glycine-NaOH (20 parts N glycine)
      (80 parts N NaOH)
   d. 6 parts redistilled acetone

B. Extraction
1. Mix 4.5 ml. of blood with 0.5 ml. 3.8 per cent Na citrate
2. Centrifuge at 2,000 r.p.m. for 10 minutes
3. Transfer the plasma to a clean glass-stoppered tube
4. Wash the red cells with 2 ml. 0.85 per cent NaCl; centrifuge at 2,000 r.p.m. for 10 minutes and add washings to plasma
5. Make up plasma to 7 ml. with distilled H_2O
6. The white cells are pipetted to a second glass-stoppered tube and made up to 7 ml. with H_2O

C. Digestion
1. To each tube add 0.5 ml. 2N NaOH
2. Warm at 50° C. for 20 to 30 minutes with occasional shaking
3. Add 6.5 Gm. $(NH_4)_2SO_4$ to each tube and keep at 50° C. for exactly 5 minutes
4. Warm quickly to 75° C. in boiling H_2O
5. Filter immediately to a clean tube (via Whatman No. 1) containing 1 ml. azure A solution and 1 ml. distilled H_2O
6. Mix by inversion; allow to stand for one hour with occasional shaking

D. Washing of precipitate
1. Centrifuge the heparin-dye complex for one hour at 3,000 r.p.m.
2. Aspirate supernatant and discard
3. To the residue add 5 ml. of 0.01 N HCl. Shake vigorously. Centrifuge 30 minutes at 3,000 r.p.m. Aspirate and discard supernatant
4. Continue to wash residue with 2 ml. H_2O; centrifuge as before; aspirate and discard supernatant

E. Colorimetry
1. To each tube add 10 ml. buffered solvent
2. Thoroughly dissolve the residue and transfer to calibrated cuvettes
3. Measure O.D. at wave length λ 530 on a Coleman No. 14 spectrophotometer

F. Calculation
1. A standard curve is prepared by treating varying amounts of sodium heparin in the same manner as the blood samples
2. The O.D. of the unknowns (plasma + WBC) may be compared to those of the standard in the following relationship:

$$\frac{\text{O.D. of unknown}}{\text{O.D. of standard}} \times \frac{\text{mg. of standard}}{4.5} \times 100 = \text{mg. heparin/100 ml. blood}$$

II. Protamine titration

A. To each of a series of 10 serology tubes (13 by 100 mm.) protamine sulfate (Eli Lilly and Company) solution (1 mg. per milliliter) is added in increments of 0.02 ml. (0.02 mg.) beginning with 0.02 ml. in first tube and 0.2 in the last.

B. After careful venipuncture 11 ml. of blood is added to a graduated tube containing 1.0 mg. of heparin.

C. To each of the above tubes containing protamine is added 1 ml. of heparinized blood. The tubes are inverted and allowed to stand for one hour at room temperature.

D. The result is expressed in milligrams of protamine, being read as that amount which is in the clotted tube containing the least amount of protamine.

III. Clotting time

A modification of the Lee-White method was used. After atraumatic venipuncture with the turniquet still in place, blood was drawn into a glass syringe. One milliliter of this heparinized blood was then measured into each of 3 chemically clean glass tubes (10 by 75 mm.) containing a small chemically clean glass bead. The first tube was tilted every 30 seconds until clotted at which time tilting of the second tube was begun and after that the third tube. The end point was the complete clotting of the third tube. The normal range of coagulation time by this method in our laboratory during the time this work was done was 9 to 17 minutes.

RESULTS

I. *Recovery of Heparin Added to Bank Plasma In Vitro.*—Ten determinations were carried out on a volume of blood bank plasma 21 to 28 days old. Two milliliter aliquots were used for the analysis. The remaining portion was kept in the frozen state until ready for use. Table I shows the results of the "heparin" assay method on these samples before and after the addition of heparin.

TABLE I. RECOVERY OF "HEPARIN" ADDED TO STORED PLASMA AS DETERMINED BY "CHEMICAL" METHOD OF ASSAY

NUMBER OF DETERMINATIONS	MG. HEPARIN IN 100 ML.*	MG. HEPARIN ADDED TO 2 ML.	MG. HEPARIN EXPECTED/ 100 ML.	MG. HEPARIN FOUND/ 100 ML.	PER CENT RECOVERY†
1	0.42	0.05	2.92	2.38	82
2	0.43	0.11	5.43	5.06	93
3	0.47	0.05	2.98	2.61	88
4	0.42	0.1	5.42	4.50	83
5	0.54	0.025	1.79	2.10	117
6	0.60	0.05	3.10	2.53	82
7	0.45	0.025	1.71	1.36	80
8	0.50	0.05	3.00	3.19	106
9	0.54	0.025	1.80	1.38	77
10	0.49	0.05	2.99	2.53	85

*Mean = 0.49 mg./100 ml. of plasma, S. D. = 0.063 mg./100 ml., S. E. = 0.019 mg./100 ml., coefficient of variation = 15.4%.

†Mean = 89.3, S. D. = 13.1%, coefficient of variation = 14%.

The mean "heparin" level in stored plasma to which no heparin had been added was 0.49 mg. per 100 c.c. of plasma with a coefficient of variation of 15.4 per cent between samples. A mean recovery of heparin of 89.3 per cent was found.

II. *"Heparin" in Blood Before and After Therapeutic Heparin Administration.*—Forty-two individuals were investigated to establish a normal value and the extent of the subsequent recovery of varying intravenous injections of sodium heparin. In each case a blood sample was withdrawn and immediately followed with an injection of heparin. Fifteen minutes later a second specimen was obtained from another site. Table II summarizes these results.

TABLE II. BLOOD HEPARIN LEVELS BEFORE AND AFTER A SINGLE DOSE OF HEPARIN ADMINISTERED INTRAVENOUSLY

NUMBER OF CASES	DOSAGE (MG.)	MG./100 ML.* PREHEPARIN	MG./100 ML. POSTHEPARIN
5	20	0.37	0.58
20	40	0.50	0.80†
8	50	0.51	0.78
5	75	0.46	0.88
4	100	0.52	1.12

*Mean = 0.48 mg./100 ml. whole blood (42 "normals"), S. D. = 0.10 mg./100 ml. blood, coefficient of variation = 20.8%.

†Mean = 0.80 (20 cases after 40 mg. intravenously), S. D. = 0.14, coefficient of variation = 17.5%.

The normal blood "heparin" level was 0.48 mg. per 100 c.c., the coefficient of variation being 20.8 per cent on 31 specimens. This closely approximated that of stored plasma as recorded in Table I. In the blood from the treated patients the cells were carefully washed to remove adherent heparin and the washings were added to the plasma. In the experiments using stored plasma this obviously was not done. The types of specimens, therefore, are not comparable. In the determinations on whole blood the amount of "heparin" found in the white cells was about equal to that in the plasma. The fact that the white cell moiety had been eliminated should render the results on plasma equal to half those on whole blood. If the results on plasma had been expressed in terms of whole blood, this would have been the case. But since they are expressed on the basis of "100 c.c. of plasma," the results are close to those on whole blood and the similarity of the figures in Table II for blood or plasma without addition of heparin can be understood.

With the exception of the fact that there was no increase between the 40 mg. and 50 mg. doses, there was a progressive increase in plasma heparin after administration of increasing amounts of heparin intravenously.

III. *Comparison of Blood "Heparin" Levels and Coagulation Times.*—Fig. 1 shows the coagulation times plotted against the blood "heparin" levels on the patients treated with heparin listed in Table II.

There is more overlap between the tests on blood in the different dose groups when the "heparin" levels are considered than there is in the coagulation times. Three of the 5 heparin assays on blood after injection of 20 mg. of heparin fell within the normal range, or below 0.6 mg. per cent. Also, 4 of these determinations on normal blood fell above the 0.6 mg. per cent level. There was no overlap in the coagulation times between normal and heparinized patients.

IV. *Comparison of the Plasma "Heparin" Level With the Protamine Titration.*—Table III shows the effect of the addition of heparin to whole blood on the "heparin" level and on protamine titration.

It can be seen that there is variation in the normal protamine titrations in response to heparin unrelated to the dosage, whereas the response of the blood "heparin" levels is uniform and predictable.

TABLE III. PROTAMINE TITRATION AND "HEPARIN" ASSAY AFTER ADDITION OF HEPARIN TO WHOLE BLOOD IN VITRO

(4.5 c.c. Blood and 0.5 c.c. 3.8 per cent Na Citrate)

SAMPLE	MG. HEPARIN/100 ML.	MG. PROTAMINE NECESSARY TO NEUTRALIZE HEPARIN IN 1 ML. BLOOD
1	0.44	0.10
+ 25 γ heparin	0.87	0.12
2	0.44	0.10
+ 50 γ heparin	1.15	0.14
3	0.36	0.12
+ 100 γ heparin	1.54	0.12
4	0.38	0.12
+ 100 γ heparin	1.45	0.14

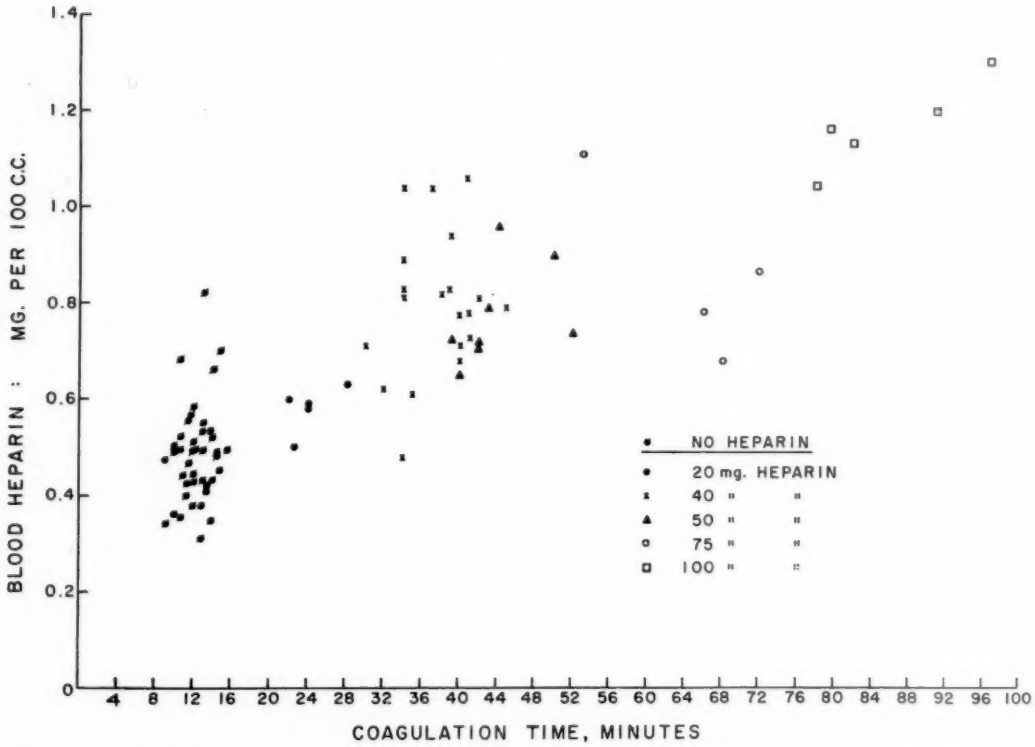

Fig. 1.—Comparison of coagulation times and blood heparin levels before and 15 minutes after injection of heparin intravenously in 42 patients.

The increase in "heparin" levels after heparin addition seems less than in Table I. Whole blood was used in these tests, whereas the work depicted in Table I was done using plasma. The adsorption of heparin to the formed elements and the inability, despite careful washing, to recover from them are possible explanations for the difference.

DISCUSSION

It is undoubtedly possible that, in the instances in which there was marked disagreement between coagulation times and blood "heparin" levels, the former

might have been wrong rather than the latter. We consider this to be unlikely, however, since in these cases the coagulation time was more nearly in conformity with heparin dosage than was the blood heparin level.

It appears that the described method of heparin assay may suffer from 2 difficulties: an inability to remove all the heparin from the formed elements of the blood and an inability to measure heparin separately from glucosamine and chondroitin sulfate.

It is probable that in this method less heparin is lost in the process of digestion from plasma protein than in others. For the recovery of heparin added to a relatively inert protein solution, it is excellent. For biologic use it is probably less practical than methods using coagulation systems.

SUMMARY

1. Experiences with Bassiouni's method of heparin assay is presented. It consists of alkalinization and heating of citrated plasma followed by metachromatic measurement of the heparin thus separated from blood proteins.

2. Of the heparin added to plasma in vitro 89 per cent was measured, making this one of the most accurate methods for in vitro recovery.

3. The method was not as accurate a measure of blood heparin levels following intravenous administration of the drug as was a carefully done coagulation time of whole blood.

4. The method appeared to be more accurate than the protamine titration method.

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THE EFFECTS OF NEOMYCIN UPON THE TOXICITY OF PERITONEAL FLUID RESULTING FROM STRANGULATION OBSTRUCTION

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THE HIGH mortality rate of strangulation obstruction continues to stand as a challenge to all interested in this condition.[7] The identity of the toxin of late strangulation obstruction has never been clearly established. Peritoneal fluid resulting from experimental strangulation obstruction of long standing is toxic when injected into normal animals.[1] The life of animals with strangulation obstruction may be prolonged by prevention of exposure to the fluid.[3] Recent experimental evidence has been obtained in our laboratory which indicated that live bacteria were partially, if not entirely, responsible for the toxicity of this material. The purpose of the following study was to determine the effects of neomycin upon the toxicity of peritoneal fluid resulting from strangulation obstruction.

MATERIALS AND METHODS

Sixty-two adult mongrel dogs were divided into 3 groups.

Group I.—The objective of the following experiment was to determine the effects of placing neomycin inside the lumen of a strangulated, closed loop of obstructed bowel upon the toxicity of the resulting peritoneal fluid. Under fractional intravenous Nembutal anesthesia, the lower ileum of 13 dogs was exposed through a midline abdominal incision. Sterile technique was utilized during all operative procedures. The venous supply to a 10 cm. segment of ileum was divided following which encircling umbilical tape ties were placed at each extremity (Fig. 1). The strangulated bowel was opened and 10 neomycin tablets (5 Gm.) were placed inside the lumen. After a 2-layer closure of the enterotomy had been effected, the bowel was returned to the abdominal cavity. The laparotomy wound was closed and the animals were returned to their cages. Forty-eight hours later they were reopened for collection of the accumulated peritoneal fluid. The fluid from each of the 3 donors was injected directly into the peritoneal cavities of 18 normal dogs in the amount of 4 c.c. per kilogram. Survival time was recorded for each recipient animal.

Group II.—The purpose of this part of the study was to determine if it were possible to alter the toxicity of strangulation obstruction fluid by placing neomycin outside the lumen but in close contact with the gangrenous bowel. A 10 cm. segment of ileum was strangulated in the manner described previously.

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The altered bowel was then placed in a plastic bag along with 10 neomycin tablets (5 Gm.). The neck of the bag was then securely fixed to normal bowel with umbilical tape ties (Fig. 2). Polyethylene bags with a capacity of one quart were used. The bag and its contents were returned to the abdominal cavity and the laparotomy incision was closed. The 3 animals which experienced this procedure were returned to their cages where they remained for 48 hours. At this time the abdominal cavity was reopened so that the bags along with the accumulated fluid could be recovered. The fluid was immediately injected into the peritoneal cavities of 8 normal dogs in the amount of 4 c.c. kilogram of body weight. Survival time was recorded for each of these animals.

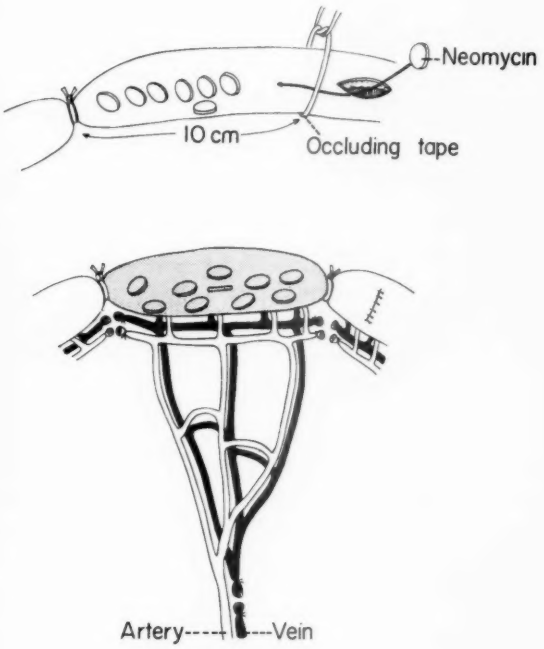

Fig. 1.

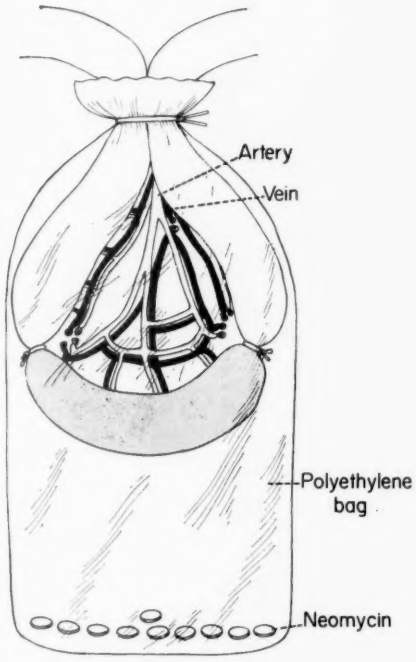

Fig. 2.

Fig. 1.—Method of introducing neomycin and producing strangulation obstruction.
Fig. 2.—Method used to expose strangulation fluid to neomycin.

Group III.—The purpose of this portion of the study was to determine if the simultaneous intraperitoneal injection of neomycin along with a toxic dose of strangulation obstruction fluid would alter the survival time of recipient animals.

Six adult dogs were anesthetized with intravenous Nembutal. A 10 cm. segment of ileum was strangulated as described in Group I but no antibiotics were used. At, or shortly before, death the accumulated peritoneal fluid was collected. Fourteen normal anesthetized animals received an intraperitoneal injection of the fluid in the amount of 4 c. c. per kilogram of body weight. Nine of the animals were also given an intraperitoneal injection of neomycin (100 mg. per kilogram). Survival time for each recipient animal was recorded.

RESULTS

Group I.—The 3 donor animals were alert and normal in appearance 48 hours after strangulation of the ileum. The peritoneal cavities of the animals contained 90, 150, and 200 c.c. of fluid, respectively. This material had the odor of fresh blood and was somewhat thicker than the fluid recovered from cases of untreated strangulation obstruction. The bowel was black in appearance but the wall was thick and tough in consistency. A small amount of fluid remained within its lumen. The unanesthetized recipient animals appeared to experience no discomfort when this material was injected into the peritoneal cavity. None of these animals died nor did they appear ill during the postinjection period (Table I).

TABLE I. RESULTS OF INTRAPERITONEAL INJECTION OF STRANGULATION OBSTRUCTION FLUID

NUMBER OF ANIMALS INJECTED	AMOUNT OF FLUID GIVEN (C.C./KG.)	CATEGORY	SURVIVORS
5	4	Unaltered fluid	0
18	4	Neomycin placed inside lumen of donor's strangulated bowel	18
8	4	Neomycin placed in plastic bag outside lumen of donor's strangulated bowel	8
9	4	Neomycin and unaltered fluid injected into peritoneal cavity simultaneously	6

Group II.—The donor animals were alive and normal in appearance 48 hours after strangulation of the bowel. The plastic bag of the 3 animals contained 175, 200, and 215 c.c. of dark fluid, respectively. The foul odor produced by the fluid of nontreated strangulation obstruction was not characteristic of this material. The bowel was black in appearance, thick walled and was without evidence of gross perforation. A small amount of fluid remained within the lumen. The unanesthetized recipient animals experienced no apparent discomfort following injection of the fluid into the peritoneal cavity. All 8 of the recipient animals recovered.

Group III.—The 6 untreated donor animals were all dead within 26 hours. Dark, foul fluid ranging in amounts from 90 to 200 c.c. was removed from the peritoneal cavity of these dogs. The strangulated bowel was black in appearance. Its wall was soft and friable in consistency. All 5 recipient animals which did not receive neomycin were dead within 12 hours. Six of the animals which received intraperitoneal neomycin recovered (Fig. 3). The 3 which failed to survive lived 16 hours, 3 days, and 4 days, respectively.

DISCUSSION

When the segment of bowel is short enough to eliminate blood loss as a significant factor, the lethal agent of strangulation obstruction arises from the lumen of the involved bowel. The survival time of experimental animals is extended by placing the altered bowel in a plastic bag so that access to the peritoneal cavity is prevented.[3] These experiments have shown that nontoxic fluid

results when neomycin is placed within the lumen of strangulated bowel. Moreover, it was possible to markedly decrease the toxicity of peritoneal fluid resulting from strangulation obstruction by injecting neomycin into the peritoneal cavities of normal dogs along with the fluid. In another experiment the lethal properties of strangulation obstruction fluid have been eliminated by high-speed centrifugation.[4] Myriads of bacterial cells were found in the toxic centrifugate. *Proteus vulgaris,* beta hemolytic streptococcus, *Escherichia coli,* and *Clostridium welchii* have been identified in this material. These findings along with the experience of others[5] emphasize the importance of bacteria in the lethal issue of strangulation obstruction.

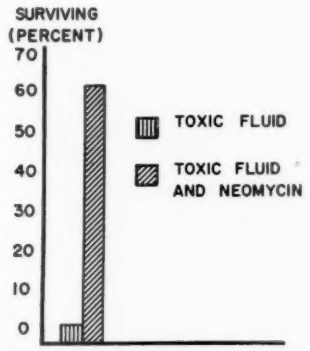

Fig. 3.—Comparison of survival rates in control animals and those treated with neomycin following intraperitoneal injection of strangulation obstruction fluid.

Another consideration of interest is whether or not the bacterial cells alone are responsible for the toxicity of the fluid or whether exotoxins also play a role. Qualitative tests have indicated the presence of the alpha toxin of the *Clostridium welchii* in peritoneal fluid resulting from strangulation obstruction.[6] It seems highly improbable than an exotoxin could be removed by centrifugation at speeds up to 17,000 r.p.m. That neomycin in a plastic bag outside strangulated bowel will render the accumulated fluid nontoxic has been established. This is better explained on the basis of bacteria being killed when they come through the wall of the gangrenous bowel and contact the neomycin rather than on the asumption that the antibiotics neutralize an exotoxin. Furthermore, in vivo physiologic studies have shown that a leukopenia follows the injection of the toxic products of strangulation obstruction while a leukocytosis follows administration of the alpha toxin of the *Clostridium welchii.*[2]

These studies suggest that intraperitoneal antibiotics in high concentration might neutralize the accumulated toxic products of strangulation obstruction and serve as a valuable adjunct to intestinal resection in the treatment of this condition. This phase of the problem is currently under investigation.

CONCLUSIONS

1. The peritoneal fluid of animals with late strangulation obstruction is toxic when injected into the peritoneal cavity of normal animals.

2. If neomycin is placed within the lumen of a closed loop of strangulated bowel, the life of the animal is prolonged. Peritoneal fluid collected 48 hours after strangulation of the bowel is nontoxic.

3. It is not necessary to place the neomycin inside the lumen of the bowel to collect nontoxic fluid. When strangulated bowel is placed in a plastic bag along with neomycin, nonlethal fluid results.

4. The intraperitoneal injection of neomycin along with toxic strangulation obstruction fluid improves the survival rate.

5. The important role of bacteria in the lethal issue of strangulation obstruction is supported by these findings.

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PRELIMINARY STUDIES ON A NEW INTESTINAL BACTERICIDE—SOFRAMYCIN

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DUE TO the inability of any one of the currently available antimicrobial agents to completely eradicate or suppress the growth of intestinal microorganisms, there is continued need for critical investigations of new agents and various combinations of antibiotics as they are developed.[1, 2, 4, 5] Poth[3] has indicated that neomycin with phthalylsulfathiazole is the best combination now available and is better than either one alone. He further stressed that, due to variations in outgrowth of certain organisms, bacitracin, *Lactobacillus acidophilus,* or antifungicidal agents may be needed to supplement the main suppressive agents.

The core of the problem is not necessarily complete suppression of the patient's fecal microflora, but obtaining a clean, fecal-free bowel together with a prolonged reduction in the numbers of prevalent organisms, so that the atraumatic and open surgical procedures can be carried out and wound healing be anticipated with a minimal morbidity from the local effects of infection. To insure this the antimicrobial agent must be capable of effecting bacterial suppression, not only at the time of surgery, but during the postoperative period when the anastomosis or intestinal wound is held only by sutures and a serum coagulum. This coincides with the period of intestinal decompression by nasogastric tube when the patient has no oral intake. During this period inadequate decompression with dilation of the bowel may result in rapid dilution of the residual antibacterial material. Thus, organisms from the intestinal crypts may overgrow and predominate if they are resistant to residual drug in the bowel.

It is our contention, furthermore, that the antimicrobial agent should be capable of significantly lowering the total bacterial population of the colon in 48 hours or less. Irrigation of both afferent and efferent loops with the antibacterial solution at the time of surgery should further suppress the number of survivors. If possible, small doses should be given via the intestinal decompression tube after operation, thus preventing overgrowth during the healing stages of the intestinal wound.

We are concerned that prospects of tailoring a multiplicity of agents and a variety of techniques to each patient will only confuse the attending personnel,

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especially where bacterial culture control of fecal material is impractical. Thus, attempts made at intestinal antisepsis will be poor and confidence in expected effects unjustified.

In light of the afore-mentioned, we have subjected a new antibiotic, framycetin sulfate,* which has a broad spectrum of activity, to a laboratory and clinical evaluation.

MATERIALS

This new antibiotic was isolated from *Streptomyces lavendulae* and given the name "framycetin sulfate." Framycetin sulfate is a white, odorless powder that is soluble in water. The material produces no toxic effects on the hematopoietic, hepatic, renal, cardiovascular, or nervous systems in therapeutic dosages administered orally. There have been no untoward effects attending oral use in effective dosage levels except for nausea in rare instances.

The drug is readily absorbed into the general circulation following administration via the subcutaneous or intramuscular routes. Absorption from the gastrointestinal tract is minimal. The antibacterial spectrum of framycetin differs in some respects from antibiotics presently used. This antibiotic has been found to have a striking inhibitory action on *Bacillus pyocyaneus* and on *Bacillus proteus.*[4] The initial tests on *Staphylococcus aureus* indicated a high degree of sensitivity on a large number of strains from clinical sources. The drug has also strong activity against the usual gram-negative fecal flora and, in our studies, against clostridial species.

METHODS

This study was carried out on the Surgical Service of St. Vincent's Hospital in New York City. The patients first selected were those with normal gastrointestinal tracts. This group was classified as "controls." They were further catalogued into 2 series. In the first, consisting of 12 patients, framycetin was given without mechanical cleansing of the colon and the diet was not restricted. The second series consisted of a group of 4 patients who received, along with framycetin, mechanical lavage, cathartics, and a low residue diet.

To this "control" group, the drug was given for 48 hours in 3 dosage levels, 250 mg. every 6 hours, 500 mg. every 6 hours, and 500 mg. every 4 hours. Additional studies for comparison were carried out in 7 other patients with neomycin in accordance with regimen stated by Poth.[3]

A second group of 22 patients in whom framycetin was evaluated all had lesions of the large bowel. These lesions consisted primarily of carcinoma with varying locations in the bowel. Some involved closure of colostomies, hemorrhagic colitis, and diverticulitis with all degrees of obstruction. In all instances the patients received 48 hours of framycetin concomitantly with the usual preoperative mechanical cleansing. A minimum of 7 doses of framycetin was given prior to surgical intervention. Bacteriologic studies were made daily of the fecal flora by serial dilution and chamber counts. Anaerobic cultures were made in each instance. Cultures were made also on Sabouraud's

*Framycetin sulfate was supplied as Soframycin by the Roussel Corporation, New York.

broth media for yeasts. At the operating table, cultures were taken from the bowel mucosa and, where feasible, a small mucosal tissue slice was taken for culture.

RESULTS

Of the 45 patients (including 7 who received neomycin) covered by this study, 21 had normal intestinal tracts but were hospitalized for other non-related conditions and served as "controls." Of these, a first series of 16 patients was given framycetin with various dosage time intervals. In this manner, the optimal preoperative regimen was established at 1.0 Gm. every 6 hours for at least 8 doses coupled with cathartics (if possible) and daily colon lavage.

The results in this group demonstrated that preoperative preparation of the normal gastrointestinal tract with framycetin was efficient and safe. Moreover, overgrowth of yeast was noted infrequently. This is in contrast to experience with other intestinal bacteriostatic and bactericidal agents. In 3 of our patients in whom culture of yeasts was reported, there were no clinical manifestations of such infestation, that is: anal pruritus, perianal inflammation, or diarrhea.

In only 4 patients were organisms present (up to 10^3 per gram of stool on the third day). In 2 instances the organisms were gram-negative and these showed some increased resistance to framycetin. In the remaining 2 patients dietary violations were reported which may have contributed to failure of complete bacteriostasis.

A second group of "controls" comprising 7 patients were given neomycin. Two patients who were given 0.5 Gm. every 4 hours revealed *Escherichia coli* present in counts up to 10^3 on each instance with neomycin-resistant colonies noted. Two other patients in this series were given neomycin (1.0 Gm. every 4 hours for 8 doses) and the 72-hour cultures demonstrated no bacterial growth. In a fifth patient, neomycin (0.5 Gm.) was given every hour for 4 hours, then every 4 hours for a total of 10 doses in 48 hours. While both gram-negative and gram-positive organisms were reduced in 48 hours from 10^8 to 10^4, the 72-hour culture demonstrated an increase in bacterial counts of *Escherichia coli* to 10^7, *Streptococcus faecalis* to 10^6, and the continued presence of hemolytic streptococci at 10^2 per gram of stool. A sixth and seventh patient, respectively, were given 0.5 Gm. of neomycin combined with 0.5 Gm. of framycetin every 4 hours. In one patient the results were good with complete suppression of bacteria in 72 hours. The other patient demonstrated no suppression whatsoever of either gram-positive or gram-negative flora.

In the 24 operative patients who received framycetin, 10 were given a 0.5 Gm. dose every 6 hours (Table I). In 9 of the remaining 14 patients, 3 patients received 1.0 Gm. every 4 hours, three 1.0 Gm. every 8 hours, two 0.5 Gm. every 4 hours, and one 0.5 Gm. every 6 hours. Five other patients received 0.5 Gm. every hour for 4 hours and then 0.5 Gm. every 4 hours for at least 10 doses. Studies are still in progress relative to results in additional patients undergoing preoperative preparation in this last series.

TABLE I. ANALYSIS OF TEN PATIENTS RECEIVING FRAMYCETIN (SOFRAMYCIN) PRIOR TO SURGERY

PATIENT	PATHOLOGY	RESULT OF SOFRAMYCIN ON FECAL FLORA	CLINICAL RESULT
1	Carcinoma of transverse colon	Complete	Excellent
2	Carcinoma of sigmoid with partial obstruction	Complete	Excellent
3	Partial obstructing malignancy of right colon	Almost complete (below 10^1)	Excellent
4	Partial obstructing malignancy of sigmoid colon	Almost complete (below 10^1)	Excellent
5	Chronic relapsing diverticulitis	Almost complete (below 10^2)	Excellent
6	Closure of transvervse colostomy	Little control of *Escherichia coli* (only 6 doses of drug)	Excellent
7	Urethrocolostomy carcinoma of bladder	Control up to 10^4 only (only 6 doses)	Good
8	Multiple polyps of colon	Complete control of all gram-positive organisms, poor control of gram-negative organisms (only 6 doses)	Good
9	Diverticulitis with partial obstruction, many blocked diverticuli, and a carcinoma of sigmoid colon	Only partial control 10^4 of gram-negative organisms, complete control of gram-positive organisms	Good
10	Inoperable carcinoma of left colon, colostomy	Only partial control of gram-negative and gram-positive organisms	Poor clinical result, but no infection

The largest group studies consisted of those undergoing bowel surgery after 2 days of oral 0.5 Gm. every 6 hours of framycetin (Fig. 1). It should be noted that at least 36 hours of fecal suppression was recorded after oral therapy ceased. The patients in this group are listed according to pathology and results.

Poor results are explained on the basis of either inadequate therapy (only 6 doses) or residual pools of organisms in the patient with a completely obstructed gastrointestinal tract. However, even in these patients the postoperative result of the surgical procedures employed was good with no postoperative infection.

The various regimens employed in the next 9 patients were done to evaluate whether more frequent dosage was necessary or less drug could be employed. When 6.0 Gm. daily was given on a regimen of 1.0 Gm. every 4 hours, the results were good in 2 patients with nonobstructing or only partially obstructing lesions. The only patient who demonstrated incomplete control had an almost completely obstructing lesion and *Escherichia coli* was present in large numbers on the mucosa at operation. The use of either 3.0 or 2.0 Gm. daily was remarkable in that, if the lesion was only partially obstructing, control was good: that is, at operation fecal growth of less than 10^2 per gram of stool.

In the 5 patients studied on a 4.0 Gm. daily regimen (0.5 Gm. every hour for 4 hours and then 0.5 Gm. every 4 hours for 11 doses) the results in 4 patients demonstrated excellent bacterial control. In one, coliforms were incompletely suppressed; 10^4 organisms were counted from specimens taken at the time of surgery. However, it must be stated that two of these patients had diverticulitis with minimal signs of obstruction and the other three had nonobstructing lesions of the colon. Further studies of this regimen are under way.

In none of these patients was framycetin instilled locally into the bowel lumen at operation.

No instances of systemic toxicity were encountered. Renal function was not influenced by drug therapy nor were there chemical indications of liver derangement.

In 3 patients of the operative series, yeast cells were demonstrated at or after surgery. However, there were no clinical symptoms or signs of pruritus ani, perianal inflammation, or diarrhea. No evidence of the development of mucous colitis was noted.

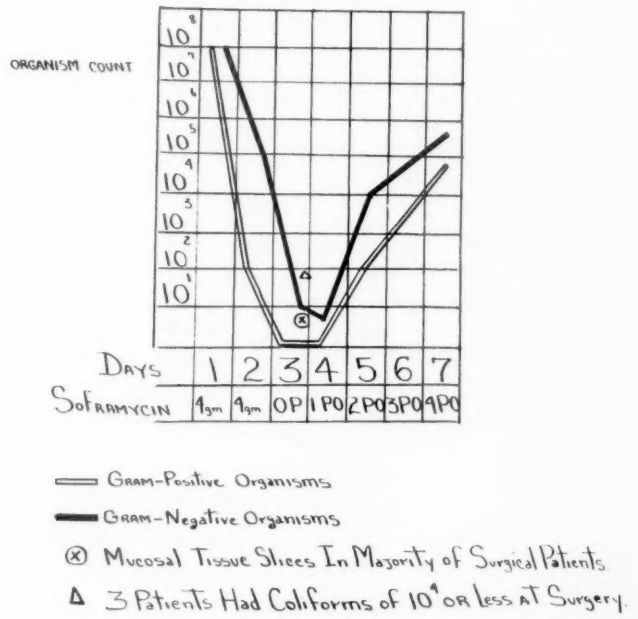

Fig. 1.—Graph of Soframycin preparation of colon in 10 patients.

DISCUSSION

The bacteriologic studies were expanded during the project to include pre- and post-framycetin therapy culture sensitivities. These studies indicated emergence of resistant coliforms if either obstructing lesions were present or drug was continued over a 5-day period. There were no indications of a similar activity as concerned the gram-postitive cocci. In almost all instances, the preoperative screening revealed sensitive strains of both gram-positive and negative flora. In 2 instances postoperatively either an *Escherichia coli* or a *Bacillus proteus* was highly resistant to framycetin in vitro.

In this study, we believe that another useful antibiotic tool for suppression of fecal flora in resection of the colon has been made available. Its merits consist of a palatable low-dosage antibiotic that is singularly nontoxic, with a wide spectrum of bacterial activity and with rapid suppressive activity during a 2-day bowel preparation. It has very few instances of predominance of yeasts concomitant with its period of activity and it appears to have a high bactericidal effect. Mucosal tissues obtained at surgery and postoperative studies indicate a high suppressive power of 36 hours after cessation of oral therapy.

SUMMARY

1. A new antibiotic, framycetin sulfate (Soframycin), for use in intestinal surgery has been studied.

2. The drug is minimally absorbed following oral therapy and is nontoxic. No untoward effects on the hematopoietic, hepatic, renal, cardiovascular, or nervous systems were found.

3. Rapid fecal suppression occurs in the nonobstructed colon on comparatively low dosages.

4. Few emergent yeast colonies are noted on the 48-hour bowel preparation.

5. At least 3.0 Gm. per day for 48 hours is optimal for adequate control. This dosage regimen is in contrast to that for neomycin, which is at least double.

6. No supplemental drug therapy such as nystatin or an insoluble sulfonamide in combination with framycetin for broader coverage seems indicated or necessary.

7. Further studies are in progress to see if better control can be secured in obstructive lesions of the colon and in diarrhea.

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FAILURE TO PROVE IDENTITY OF TUMOR CELLS IN THE PERIPHERAL BLOOD

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THERE has been considerable current interest and speculation over the finding of "tumor cells" in the peripheral circulating blood of cancer patients. This possibility has been revived and largely sparked by Engell's recent monograph.[1]

Studies of others[2-5] confirm the findings of Engell. Briefly, these indicate that many immature cells with the features of free malignant cells are found in the peripheral blood stream of patients with active cancer and are not found in the peripheral blood of normal patients.

The concept that there may be occasional showers of cancer cells in the peripheral blood is not new. It has received much speculation in the past and recent confirmation cannot be ignored. The resulting conclusions are extremely important and may alter therapeutic approach to all neoplastic disease. Therefore, definite identification of these cells is of more than academic interest.

We, too, have been fascinated in finding "tumor cells" in the peripheral blood of tumor patients (Fig. 1). They certainly look like malignant cells and we believe they are, but there is always the possibility that they are not; complete proof is lacking.

The means of definitely establishing the identity of such cells are indeed limited. However, it seemed to us that one way of proof would be to reinject the suspect cells back into the patient who produced them in the hope of producing a man-made metastasis. This had certain quite evident advantages and above all it might give actual proof, for one induced growth would equal many morphologic descriptions. We feel quite sure that this method must have been tried by others, but so far have not found any such report.

METHOD

Four patients were studied who were in the terminal phase of their neoplastic disease. All had carcinoma (lung, stomach, and colon) with widespread extension. "Tumor cells" were demonstrated in the peripheral blood of each. They died at intervals of 2 to 7 months after our investigation.

From 50 to 80 ml. of blood was drawn from the antecubital vein into a heparin solution. On 3 occasions blood was taken from the femoral artery. The blood was then spun down in long tubes (15 minutes at 1,500 r.p.m.) so that

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a definite buffy coat could be isolated. This layer has been shown to contain a high concentration of "tumor cells." It was removed and mixed with a small quantity of saline to make approximately 2 ml. This buffy coat mixture contained most of the suspicious abnormal cells present in 50 to 80 ml. of the patient's peripheral blood. Twelve such samples were withdrawn from the 4 patients.

Injections of the buffy coat mixture were then made in the patient from whom the sample was taken. For the most part, a portion was injected into a marked area of subcutaneous fat or muscle. On some occasions it was given intradermally as well as in one or more of the other sites.

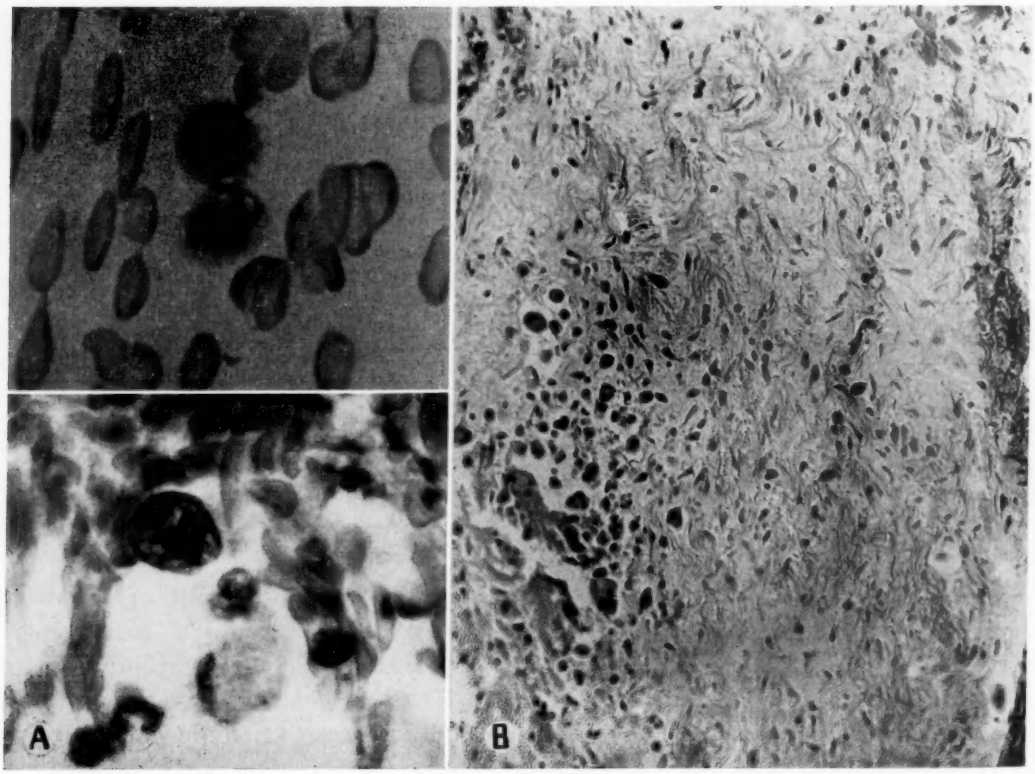

Fig. 1.—*A*, Tumor cells in smears from peripheral blood. The upper photograph shows a leukocyte just beneath a cell containing many nucleoli. (Papanicolaou stain, ×950, 2/7 off reduction. *B*, Area of fibrosis from host showing macrophages and foreign-body giant cells resulting from injection of buffy layer mixture. (Hematoxylin and eosin stain, ×125, 2/7 off reduction.)

RESULTS

The injection resulted in a definite local lump. This was observed to diminish in size until no palpable nodule was present 2 months after injection. Likewise, no new nodule appeared which might suggest a new growth.

After death (2 to 7 months), the tissues at the injection site were removed for study. Often the tissues showed little or no gross abnormality. Under microscopic examination there were a little fibrosis, hemosiderin, foreign-body

giant cells, and occasionally in the early lesions there were nuclear fragments (Fig. 1). There was, however, never any evidence of tumor cells at the site of injection.

DISCUSSION

This failure to reproduce tumor growth from suspect tumor cells in the peripheral blood stream neither proves nor disproves them to be circulating cancer cells. There are many reasons why these cells injected into their host might not reproduce a secondary lesion. A few of these should be mentioned.

First of all, the number of "tumor cells" actually collected in the buffy coat in this experiment was comparatively small. It is estimated that a few hundred were concentrated in each injected blood sample. How many hundreds is pure conjecture but certainly not the extremely large numbers required to reproduce some types of experimental tumor transplant.

Second, the "tumor cells" of necessity were collected and injected into the host with huge numbers of leukocytes. It seems very likely that as this mass of leukocytes undergoes degeneration, various ferments are liberated which are highly detrimental and lytic to all cell protoplasm. The tumor cells might well be lysed as a result.

Third, the host must have a considerable ability to eliminate stray tumor cells, for if it could not and these are truly tumor cells then metastases would indeed be unlimited. The elected sites of injection (skin, subcutaneous fat, and muscle) may not have been ideal though we have no better suggestion. Perhaps, after all, an attempt to grow these tumor cells in vitro would be more logical. Certainly any further work along the present lines must include a more pure concentrated mass of cells to be tested.

It may be rather naïve to expect a metastatic reproduction from the procedure here outlined. On the other hand, we have repeatedly transplanted experimental tumors with only a fraction of the number of cells thought to be inoculated by the present transfer. Also, the number of tumor cells necessary for an accidental autogenous wound implant or gut anastomosis implant are thought to be rather few as compared with those used in our trial.

What happens to all these circulating "tumor cells"? We have never identified or recognized any cells being phagocytized or undergoing degenerative changes.

Our negative findings have been very disappointing. No amount of surmise or speculation about morphology can be half as convincing as the actual production of a metastatic lesion. We believe these must be cancer cells, but the final proof is lacking.

SUMMARY

An attempt was made to establish the identity of "tumor cells" appearing in the blood stream of patients with active cancer by injecting these cells into their host.

No secondary tumor growth resulted.

This negative report by no means rules out the validity of the assumption that these immature circulating cells are cancer. It is important to establish more than morphologic proof of this concept.

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RESULTS OF TREATMENT OF CYSTIC DISEASE OF THE BREAST

Five- to Eighteen-Year Survey

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THE symptom complex of cystic disease of the breast is the most frequently encountered entity in the management of diseases of the mammary gland. Recognition of the probable etiology, gross and histologic types, and clinical manifestations is essential to the physician, surgeon, and pathologist in the proper treatment of this disease. A lack of standardization of terminology applied to cystic disease since it was first described clinically over a century ago by Cooper[10] and Brodie[6] and the diverse opinions of authors concerning its etiology, pathology, precancerous nature, and the influence of estrogenic hormones upon it have caused confusion in this type of mammary gland pathology.

The purpose of this report is to present the findings in 484 private female patients with cystic disease of the breast treated from 1933 to 1951, including the clinical histories, operative findings, pathologic reports, therapy administered, and follow-up examinations on 432, or 90 per cent, of the group. This investigation was undertaken, not in an attempt to present solutions to the yet unsolved problems of cystic disease of the breast, but to report various gross and histologic manifestations of the disease observed in this series of patients and to evaluate the results of conservative therapeutic measures utilized in their treatment. Consideration is also given to certain factors which presented themselves that could be of etiologic significance to the disease and its possible relation to malignancy.

INCIDENCE

It is impossible to determine, with any degree of accuracy, what percentage of the adult female population is affected with cystic disease of the breast since most women have some pain in the breast occasionally and in the majority of female breasts the lobules are normally firmer than those in surrounding subcutaneous tissue. Also, those patients with microscopic cysts escape detection by routine methods of examination. Goldberg and associates[14] have established that approximately one of every 20 women in the state of New York develops carcinoma of the breast in a lifetime. Since clinical evidence of cystic disease of the breast occurs more frequently than carcinoma, it would be a safe assumption that one of every 15 women in the general adult population develops clinical evidence of cystic disease of the mammary gland in a menstrual lifetime.

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In a study by Franz and associates[12] of mammary gland tissue without clinical evidence of abnormality in 225 women at autopsy, macroscopic cystic disease (cysts 1 to 2 mm. or more in diameter) was observed in 19 per cent. Microscopic cystic disease, evidenced by apocrine metaplasia of duct epithelium, intraductal epithelial proliferation, and microcysts (those less than 1 mm. in diameter), was observed in 34 per cent. The abnormalities were bilateral in approximately 50 per cent and some form of the cystic disease complex was present in 53 per cent of all subjects studied.

Foote and Stewart,[11] in an investigation undertaken primarily to determine if fundamental structural differences exist in breast tissue of women with mammary cancer and those without the disease, examined 300 breasts containing carcinoma and 200 specimens of noncancerous breast tissue and found lesions they considered to be diagnostic of "chronic cystic mastitis" in 83 per cent of the 300 cases of mammary carcinoma while the incidence in the 200 noncancerous specimens was 90 per cent.

Franzas,[13] in a study at autopsy of the breasts of 100 women between the ages of 19 and 90 years, found microscopic cystic disease in 55 per cent; the disease was bilateral in 25 per cent of the specimens. During the period that this group of 484 patients were treated for cystic disease of the breast, intraductal papilloma was encountered in 204 and 452 were observed with primary carcinoma.[18, 19]

AGE DISTRIBUTION

The highest incidence of cystic disease of the breast was observed between the ages of 40 and 49 years; 45 per cent of the patients were in this range. Fourteen patients, or 3 per cent, were past the age of 70 years, but, in all probability, these patients either had cystic disease before menopause or had received estrogenic therapy not recorded in their histories prior to the time a diagnosis of cystic disease was established.

The highest incidence of cancer of the breast in 452 patients with primary carcinoma observed during this period was also between the ages of 40 and 49 years. However, the age distribution in carcinoma was higher past the age of 49 years than that of cystic disease (Table I).

TABLE I. COMPARISON OF AGES OF PATIENTS WITH CYSTIC DISEASE AND PRIMARY CARCINOMA OF THE BREAST

AGE (YEARS)	PATIENTS WITH CYSTIC DISEASE OF THE BREAST		PATIENTS WITH PRIMARY CARCINOMA OF THE BREAST	
	NUMBER	PER CENT	NUMBER	PER CENT
10-19	5	1.0	2	0.4
20-29	29	6.0	8	1.8
30-39	143	29.5	68	15.0
40-49	221	45.7	141	31.2
50-59	53	10.9	136	30.1
60-69	19	4.0	72	15.9
70 plus	14	2.9	25	5.5
Total	484		452	

MARITAL STATUS AND PREGNANCY

Twenty-two per cent, or 126 patients, were unmarried with no history of pregnancy and 10 per cent, or 48 patients, were married with no history of pregnancy. Forty-two per cent, or 202 patients, had a history of one or more pregnancies. Ninety patients had incomplete histories concerning marital status and pregnancy. In 66 patients in whom adenosis was part of the cystic disease complex, sterility was frequent.

ETIOLOGY

There is no agreement on the etiology of cystic disease of the breast at this time; current considerations are, for the most part, theoretical and serve only to stimulate further inquiry. König,[22] an early investigator of breast diseases, was of the opinion that cystic disease was not neoplastic in origin but resulted from an inflammatory reaction and he designated the disease "chronic cystic mastitis." This term suggests very little concerning the histologic characteristics of the disease but has been widely used; it has probably been the most significant factor in a general misunderstanding of cystic disease of the breast because of the assumption that the disease is inflammatory in origin. A better understanding of the disease would be greatly facilitated by a name designating more definite pathologic processes encountered in it.

A great amount of experimental work, most of which has been concerned with the effects of estrogenic hormones on breast tissue, has been undertaken in at attempt to establish the presence of certain etiologic factors in cystic disease of the breast.[2, 15, 17, 21, 23] Lewis and Geschickter[23] demonstrated that intense unopposed estrogen stimulation results in epithelial proliferation, dilatation of ducts, and formation of microcysts in breast tissue. The pioneer experimental studies of ovarian hormone effects on the breasts of mice were carried out in France in which cystic changes were produced in the mammary glands of ovariectomized mice by prolonged estrogenic stimulation.[15] Histologically, this process is similar to that observed in cystic disease in the human except that in mice the changes usually involve the entire mammary gland while in the human, in most instances, cystic disease is localized to one segment of the breast. Haagensen and Randall[17] found that a marked difference existed among different strains of mice in their tendencies to develop cystic changes following the administration of estrogenic hormones.

Kier and associates,[21] in a recent study of endocrine relations in benign lesions of the breast, subjected breast tissue removed for biopsy purposes to direct chemical analysis which revealed a deficit in estrogenic antagonist suggestive of a lack of progesterone. This observation propounds the question: Does excessive estrogenic stimulation stem from estrogenic secretion or a decrease of a substance physiologically antagonistic to estrogen? Further, these investigators studied fresh biopsy material from 15 consecutive patients in whom breast lesions and endometrium were reviewed simultaneously and found there were frequent associated abnormalities in the endometrium suggestive of ovarian dysfunction of a nonovulatory type.

PATHOLOGY

The most common form of cystic disease is a localized area of nodularity usually in the upper outer quadrant of one or both breasts. These nodularities vary from 1 to 2 mm. to 1 or more cm. in diameter. In 266 patients whose ages ranged from 35 to 44 years, the disease was localized to one segment of the breast; the majority of these patients had large breasts.

In 52 other patients whose breasts were smaller than those referred to above and firm, granular, or nodular, there was diffuse involvement of one or both breasts with one area in which the disease was more pronounced. Histologic examination of biopsy material revealed areas of adenosis throughout the section in most cases. The majority of these patients who were unmarried or, if so, had a high incidence of sterility gave histories of menstrual irregularity, mastodynia, and dysmenorrhea in the early period of menstrual life.

Fig. 1.—Large discrete cyst which was well delineated, movable, and fluctuant involving medial quadrant of left breast; 80 c.c. of straw-colored fluid as removed from the cyst by aspiration. There was no recurrence after 15 years.

When a discrete cyst is present the gross appearance of the breast varies with the size of the cyst and its histologic structure. When it is superficially located it is usually round, well delineated, and movable in the surrounding breast tissue simulating an adenofibroma in this respect in contrast to a carcinoma. If it is located on the posterior aspect of a large thick breast (Fig. 1), it may be difficult, clinically, to differentiate from carcinoma because there may be retraction of the skin over the cyst with very little fluctuation. A discrete cyst is usually associated with numerous smaller cysts involving the same segment of breast tissue. The consistency of a discrete cyst depends upon

the pressure of fluid within it; if the pressure is low, fluctuation can be detected but, if the pressure is high, the cyst is firm. In older patients with atrophy of the mammary tissue, the tissue adjacent to the cyst is distorted and there is retraction of the skin over the cyst simulating carcinoma, especially if the cyst has been present for a number of years. The walls of such cysts are usually thickened and the consistency is firm but not hard. Most larger cysts are located medially and apparently develop from obstruction of larger ducts. When exposed at the operating table they are dark bluish in color which prompted the name "blue-dome" cyst of Bloodgood.[4] When such a cyst is aspirated, the color of the fluid recovered varies from straw brown, to almost black; when it is opened at the operating table the wall is thick, smooth, and glistening. However, if it has been present for a long period of time, there may be some trabeculation and thickening of the wall. There were 167 patients in this series with discrete cysts varying in size from 3 to 14 cm. in diameter; the majority of these patients were past the age of 42 years.

The histologic features of cystic disease of the breast are divided into 5 groups.

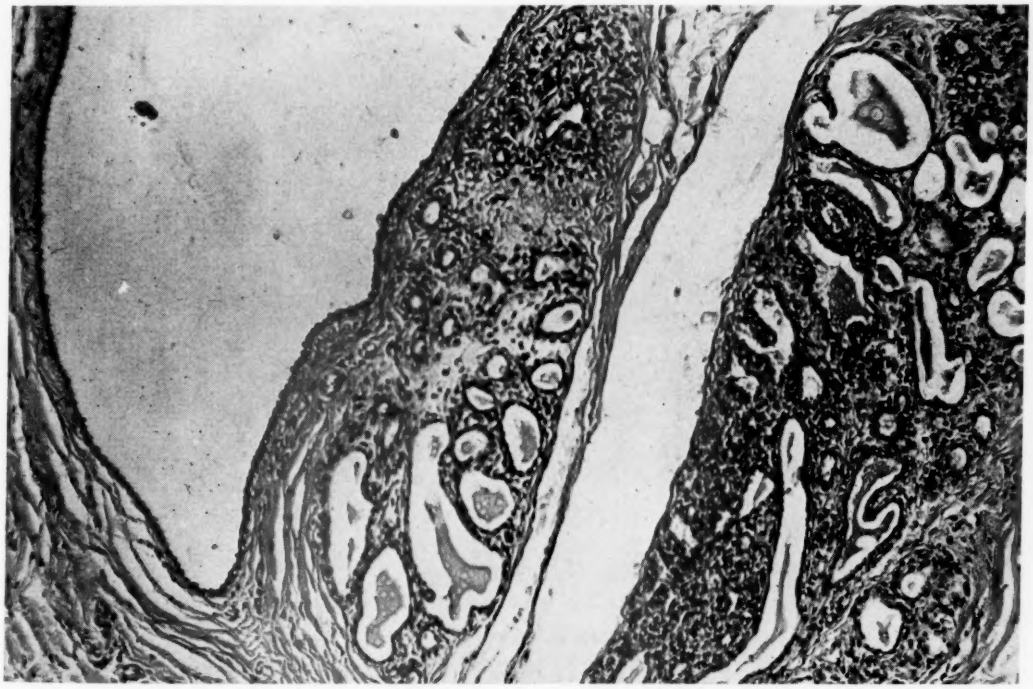

Fig. 2.—Photomicrograph of cystic disease demonstrating epithelial proliferation; cyst is lined with pavement epithelium and multiple small cysts contain cellular debris; dilated duct has thickened wall.

1. Proliferation of the Epithelium.—Epithelial cells lining the ducts and alveoli undergo marked proliferative changes and multiply to the extent that, instead of being 2 rows thick, frequently the smaller ducts and alveoli are studded with proliferative cells (Fig. 2). The proliferative epithelium may produce a papillary pattern consisting of irregular papillations which form

lacelike or glandular patterns. Some such papillations have thin stalks, as shown in Fig. 11, while others have thick stalks containing fibrous tissue and blood vessels producing intracystic or intraductal papillomas, as shown in Fig. 5.

The top layers of the proliferative epithelium become desquamated and the cast off cells disintegrate into an amorphous debris filling the ducts and resulting in the formation of small cysts, as shown in Fig. 9. When larger ducts and acini are involved by a marked proliferative process the ducts are distended with proliferative cells which may show irregularity in form and staining ability but the basement membrane remains intact. This histologic picture may simulate intraductal carcinoma but careful study of the individual proliferative epithelial cells will demonstrate their benign characteristics.

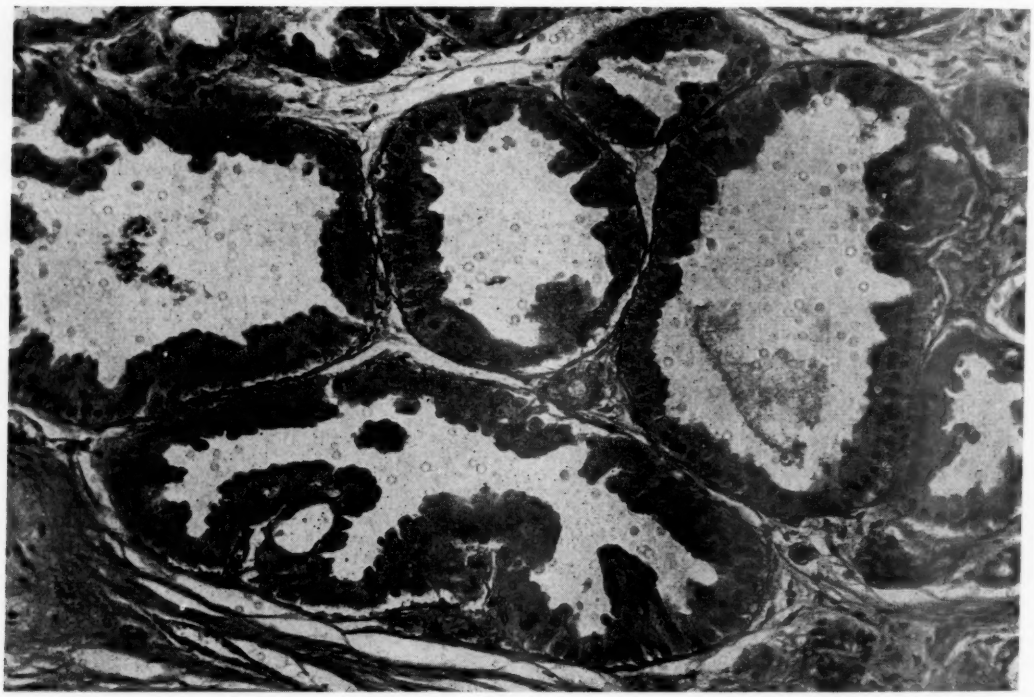

Fig. 3.—Photomicrograph demonstrating multiple microcysts lined with apocrine epithelium.

2. Metaplasia of the Epithelium.—In most biopsy specimens of cystic disease of the breast, large pale cells, one layer in thickness, are observed with pale staining eosinophilic cytoplasm. Occasionally these cells develop papillomatous projections (Fig. 3); they are apocrine in their mode of activity in that the most peripheral portion of the cytoplasm is squeezed off as a secretion into the lumen of the ducts. Apocrine epithelium was formerly regarded as a serious omen but experience has proved this to be untrue. What stimulus produces metaplasia of the cuboidal epithelium of the ducts and acini is not evident.

Frequently numerous small cysts lined with apocrine epithelium one layer in thickness are observed and it is not uncommon to observe microscopic or macroscopic cysts or dilated ducts which contain proliferative epithelium forming papillomatous projections as well as metaplasia of the epithelium into

the apocrine type. Such a histologic picture may stimulate a malignancy on frozen section and may be interpreted as such by less experienced pathologists, thereby subjecting the patient to a radical mastectomy in which case all are safeguarded except the patient who undergoes the surgical procedure. The true nature of this histologic picture is determined from the permanent sections and depends upon the integrity of the basement membrane, staining properties of the nucleus, the number of mitotic figures present, and other morphologic characteristics, as shown in Fig. 9. As Atkins[1] has wisely commented, "Malignancy is a mode of behaviour and not a histologic concept."

In reviewing the histology of 200 of the 452 patients with primary carcinoma of the mammary gland observed during the same period of this series of patients with cystic disease, 120 were found to have cystic disease of the breast in addition to carcinoma, and apocrine epithelium was present in the majority of sections that contained cystic disease in those patients.[19]

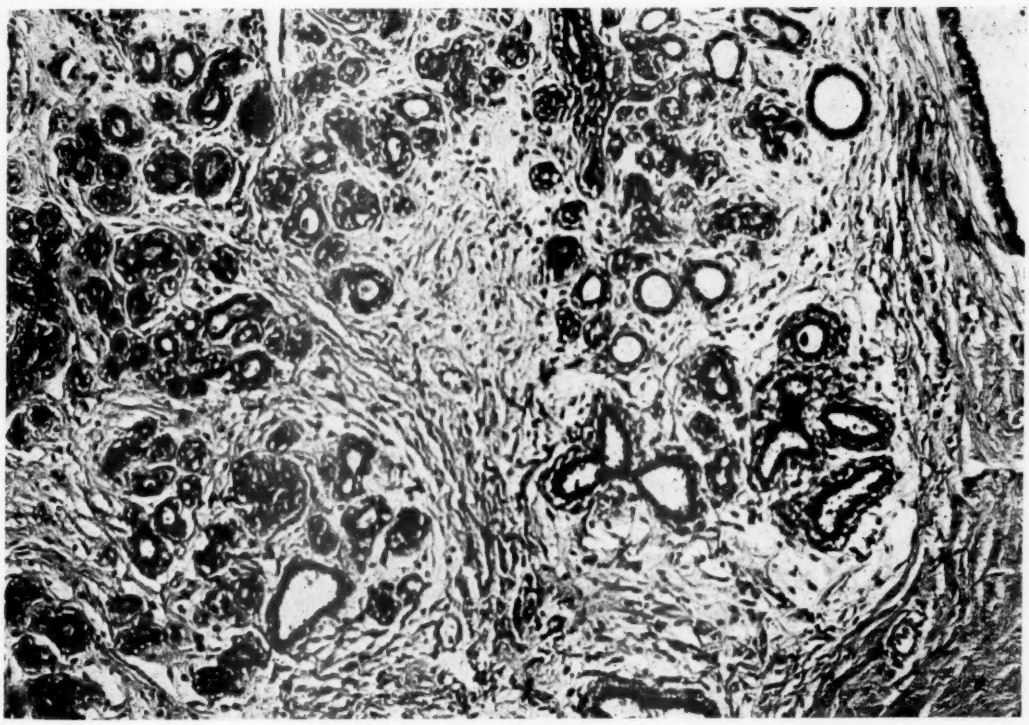

Fig. 4.—Photomicrograph demonstrating multiple microcysts, small dilated ducts, and epithelial and fibrous tissue proliferation in the adenosis form of cystic disease in a 34-year-old patient.

3. Micro- and Macrocysts.—The term "microcyst" is used to designate dilated ducts and cysts not visible grossly. It may be difficult to differentiate between micro- or small macrocysts and dilated ducts (Fig. 4). Cysts have thinner walls than ducts; frequently, for the reason that they are so numerous, as shown in Fig. 7, the dilatations must represent acini. It is not known by what process cysts develop. Cheatle and Cutler,[7] by studying the surrounding connective tissue, concluded that the origin of microcysts is in the acini exclusively. Some histologic sections show microcysts lined by a pavement type

TABLE II. TYPES OF NIPPLE DISCHARGE IN 1,361 LESIONS OF THE BREAST

DIAGNOSIS	TOTAL NUMBER OF PATIENTS	WHITISH	BROWNISH	BROWNISH-GREEN	SEROUS	SEROSANGUINEOUS	BLOODY	TOTAL NUMBER OF PATIENTS WITH DISCHARGE
Cystic disease	484	24	38	66				128
Carcinoma	452	20	24		13	2	10	69
Intraductal papilloma	208		20	28	12	34	146	240
Fibroadenoma	104	8	13	8				29
Localizing adenosis	38	4	14	6				24
Ectasia of the ducts (comedo or plasma cell mastitis)	22		4	14				18
Fat necrosis	12	2	3	3				8
Chronic abscess	41	4	8	9	18			39
Total	1,361	62	124	134	43	36	156	

epithelium, as shown in Fig. 2; other sections show marked hyperplasia and metaplasia of the epithelium completely filling the dilated ducts. Lymphocytic infiltration around the duct walls probably results from irritation by desquamated cells (Fig. 5). If such dilated ducts are in the proximity of the areolae and the duct systems are patent, the patient usually has a nipple discharge; on the other hand, if the duct system is closed, a macrocyst develops.

When the biopsy specimen is sectioned at the operating table, frequently thick material, comparable to toothpaste and varying in color from creamy, yellow, yellowish, or olive green to chocolate, will exude from the dilated ducts or macrocysts which may be more numerous in some areas of the specimen than others. The remainder of the tissue is pale, whitish pink, or grayish white and glistening and contains smaller ducts which appear as bluish dots on the cut surface with an occasional small blue-dome cyst with a thick wall which may be considered an innocent bystander with no special significance in the proliferative process.

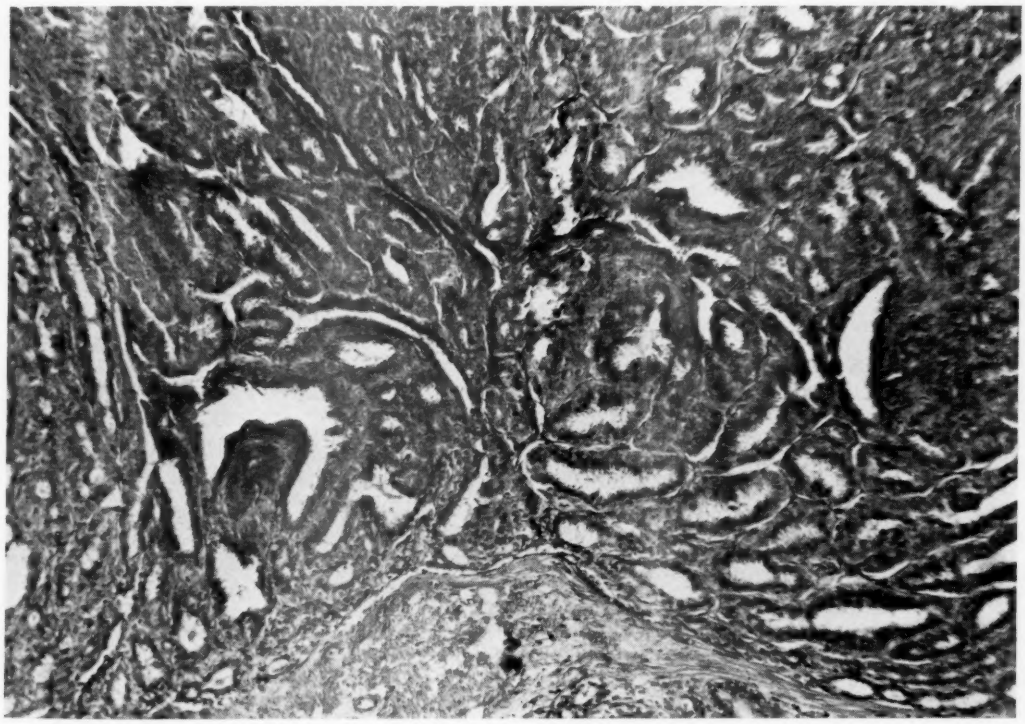

Fig. 5.—Photomicrograph demonstrating marked epithelial proliferation; the ducts are filled with papillomatous projections with broad bases in the same patient as shown in Fig. 4, 10 years later at the age of 44 years. The benign lesion frequently is mistaken for malignancy on frozen section.

This histologic feature of cystic disease permits the experienced surgeon to differentiate cystic disease from carcinoma of the breast at the operating table; cystic disease does not have the gross appearance of a carcinoma. There is an absence of the chalklike streaks which are characteristic of carcinoma.

There were 128 patients in this group who had nipple discharge at the time of the initial examination (Table II). In 24 patients the discharge was

whitish in color; in 38, it was brownish; and, in 66, it was brownish green. Serosanguineous or bloody nipple discharge, which denotes intraductal papilloma,[18] was not observed in any patient with cystic disease.

4. Mesenchymal Changes.—It is an accepted fact that the stimulus that produces epithelial proliferation and metaplasia of the epithelium also initiates proliferation of the fibrous tissue components beyond normal. Fibrous tissue activity is demonstrated in the early stage of cystic disease by the presence of an abundance of fibroblasts containing deeply staining nuclei, as shown in Fig. 4; in a later stage, when the patient is in the early forties, the staining properties of the connective tissue are less prominent and the nuclei are more widely spaced, as shown in Fig. 9. When the patient is observed at the age of 60 years, the fibrous tissue has lost all evidence of activity and, histologically, only eosinophilic collagen fibers with an occasional isolated nucleus are observed (Fig. 6). The natural history of the stroma of the breast has been

Fig. 6.—Photomicrograph demonstrating epithelial tissue almost completely replaced with inert collagen fibers in the same patient as shown in Figs. 4 and 5, at the age of 60 years; only an occasional isolated nucleus remains indicating the endocrine fires have burned out.

described simply by saying that the fibroblasts, which are plump and vigorous with deeply staining nuclei, become fibrocytes infused with the lethargy of adults who have attained and passed their prime, eventually deteriorating into inert collagen fibrils like wraiths haunting the scene of their former activities.[1]

The author has observed that patients who complain of excessive pain in the breasts during early menstrual life show excessive fibroblastic activity when sections are taken for biopsy. Histologic examination of sections of mammary

tissue in these patients taken years later shows only masses of inert collagen fibers remaining; the pain has disappeared and the fires of the epithelial and mesenchymal tissues are burned out. It would seem that, on the whole, life is a span in which we are getting ourselves generally fibrosed although we cannot point to any particular or single organ as the chief target of the process.

5. Adenosis.—Adenosis, which is a term denoting multiplication of the terminal ducts and acini, is a histologic feature observed in most cases of cystic disease of the breast and is characterized clinically by multiple nodules in one or both breasts varying in diameter from 1 mm. to 1 cm. Adenosis may form a localized tumor but not as well delineated as a gross cyst. The majority of patients with this form of cystic disease are childless with menstrual irregularity, mastodynia, and evidence of nervous tension. The nodularity characteristic of adenosis is more pronounced in the premenstrual period at which time the mammary tissue has the sensation of being indurated.

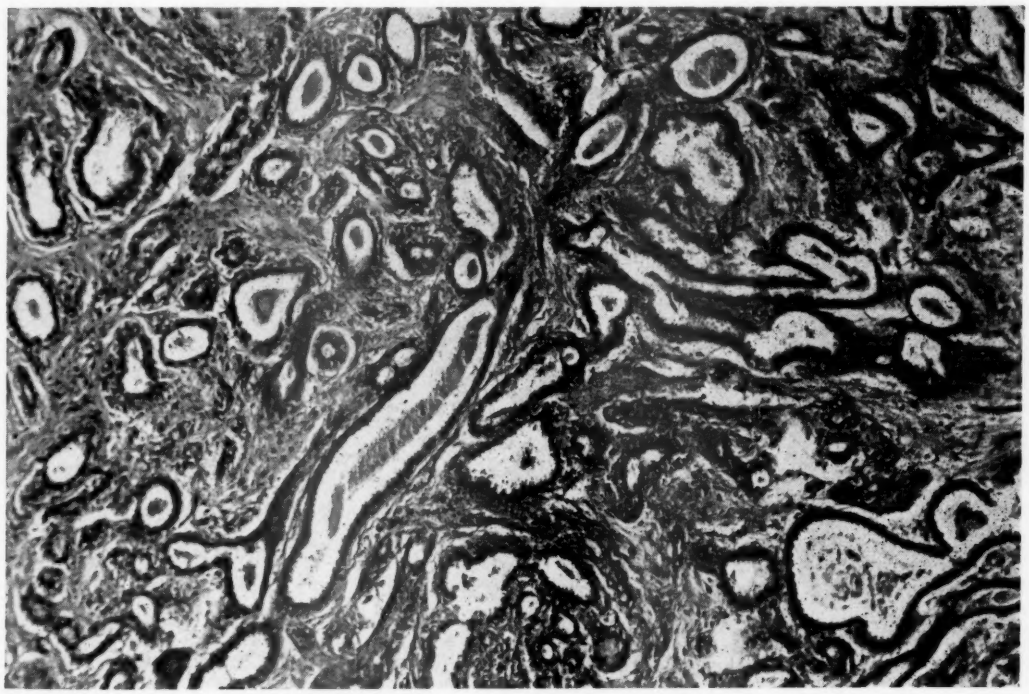

Fig. 7.—Photomicrograph demonstrating dilated acini and small ducts containing cellular debris and epithelial and mesenchymal proliferation in a patient 36 years of age with cystic disease of the breast who had had ovariectomy followed by large doses of estrogenic hormone for a period of one year.

Histologically, the involved area of tissue is riddled with minute cysts and dilated ducts demonstrating marked epithelial proliferation with an increase in fibrous tissue (Fig. 7). Copeland[9] states that apparently adenosis, which is an extremely painful condition, is produced by marked estrogenic stimulation during adolescence resulting in early sexual maturity and stunting of the breast. Two histologic types of adenosis occur[11]: blunt duct adenosis in which the small ducts multiply, and the lobular pattern of adenosis in which the acini are involved. The blunt duct type apparently results from budding of the

ductal system producing groups of small ducts without terminal lobules of acini. The newly formed ducts vary in size; the larger ones simulate microcysts. In the lobular pattern the acini appear to extend out into the breast stroma, increase in size, and multiply but retain a lobular pattern.

In adenosis, the proliferating epithelial cells vary in size and shape and frequent mitotic figures are present. Proliferation of the fibrous tissue produces separation of the acini and duct, one from another. On section, when ducts are cut obliquely, they may appear, on microscopic examination, to be scirrhus carcinoma. Sclerosing adenosis is the most frequent benign lesion of the breast mistaken for carcinoma on frozen section.

SYMPTOMS

Cystic disease of the breast is a nodular condition, frequently painful, not associated with bacterial inflammation, fat necrosis, or new growth. It frequently presents no symptoms other than a tender lump or thickened area which, when discovered by an intelligent patient, often is accompanied by anxiety. The pain, in most cases, is not severe except in younger women with adenosis; it may be present only in the premenstrual period and is probably associated with increased vascularity of the breasts produced by an endocrine stimulus resulting in fibrous tissue and epithelial proliferation. Many patients, while bathing or dressing, accidentally discover a lump or thickened area which is more tender on palpation than the remainder of the breast. A review of the histories of 167 patients in whom cysts were present of sufficient size (4 to 15 cm. in diameter) to be treated by aspiration demonstrated that it was not unusual for the observing patient to note that the lump varied in size from time to time; other patients stated that when a tumor developed rapidly it was very painful due to an increase in tension of the contained fluid.

DIAGNOSIS

Cystic disease of the breast occurs more frequently in younger patients than carcinoma and in older patients than fibroadenoma. When a large cyst is present and superficially located, fluctuation can be detected; the tumor is movable in the surrounding breast tissue and retraction is less likely to be present than observed in carcinoma. On the other hand, when there is a deeply located cyst with a thick fibrous wall, it may be difficult to differentiate from carcinoma. Fluctuation does not only indicate the presence of a cyst; occasionally a lipoma, sarcoma, or soft type of carcinoma may produce a soft, tender tumor with a smooth surface.

When there is a segment of thickened breast tissue involved, usually small cysts or dilated ducts (1 to 2 cm. in diameter) can be palpated and, as a rule, a correct clinical diagnosis can be established before surgical excision is performed when this treatment is deemed necessary.

THE RELATION OF CYSTIC DISEASE TO CANCER OF THE BREAST

The precancerous nature of cystic disease of the breast has been a subject of controversy for many years. The literature on this problem is voluminous and increasing. Some forms of cystic disease have been produced in laboratory

animals by the administration of estrogenic substances and further stimulation of some of these animals with estrogenic hormones has produced neoplastic changes which have led some observers to conclude that cystic disease is a precancerous condition in direct line with the formation of cancer. Many authors seem willing to accept this as proof that there is a direct relation between cystic disease and carcinoma, but there appears to be a suggestion of inaccuracy in such reasoning. If such investigations are to be of value, several factors must be considered, such as: (1) the innate quality of the tissue to respond to hormone stimulation; (2) the age at which the stimulus is effective; (3) a virus or other transmitting agent of the cancer[3]; and (4) the fact that some strains of laboratory animals are more susceptible to cancer than others, indicating a susceptible genetic constitution. Atkins[1] states that, histologically, the game of arranging a number of microscopic slides in a series showing a normal breast at one end, all intermediate phases of cystic disease in between, and cancer at the opposite end is one which few pathologists can resist. However, fascinating as this hypothesis may seem, it demands a great deal of imagination. It is no less scientific to conceive that the normal breast develops from cancer through all the stages of cystic disease in the reverse order.

Some authors are of the opinion that breast cancer develops more frequently in women with cystic disease than in those of comparable age without cystic disease.[8, 24, 28] Others believe that the short interval, 2 to 4 years, between the diagnosis of cystic disease and carcinoma does not rule out the possibility that cancer, in an early stage, was present when the diagnosis of cystic disease was made.[1, 16, 26] Bloodgood,[4, 5] one of the early foremost authorities on diseases of the mammary gland, commented that cystic disease was extremely prevalent during the menstrual age of women and that the disease was benign and had no precancerous attributes. He further contended that it should be treated only with conservative measures and stated that seldom should even a simple mastectomy be carried out as a method of therapy.

Stout,[26] with a vast experience in surgical pathology of the mammary gland, states that although he does not wish to imply that he does not believe that cystic disease with hyperplasia does not provide a more favorable condition for the development of cancer of the breast than its absence, he has not yet been offered proof convincing to him that cystic disease is a precancerous condition. He further states that simple mastectomy used as prophylactic treatment for cancer of the breast is a delusion.

Foote and Stewart,[11] reporting from Memorial Hospital after making comparative studies in 200 patients with benign breast lesions and 300 cancers of the breast, conclude that present data are not sufficient to determine the exact importance of "chronic cystic mastitis" in the over-all development of carcinoma of the breast.

Four patients, representing less than 1 per cent of this series, developed cancer; two had carcinomas in the same breast (Table III). The period of time between biopsy of the breast which demonstrated cystic disease and the diagnosis of cancer varied in these 4 patients from 8 to 16 years. A résumé of the history of each of these patients is given.

TABLE III. INCIDENCE OF CARCINOMA OF THE BREAST IN 484 PATIENTS FOLLOWING TREATMENT FOR CYSTIC DISEASE

PERIOD FOLLOWED (YEARS)	PATIENTS WHO DEVELOPED CARCINOMA	PATIENTS WHO DEVELOPED CARCINOMA IN THE SAME BREAST	PATIENTS WHO DEVELOPED CARCINOMA IN THE OPPOSITE BREAST	TOTAL NUMBER OF PATIENTS FOLLOWED
5-9	1	1	0	188
9-13	2	1	1	155
13-18	1	0	1	89
Total	4	2	2	432

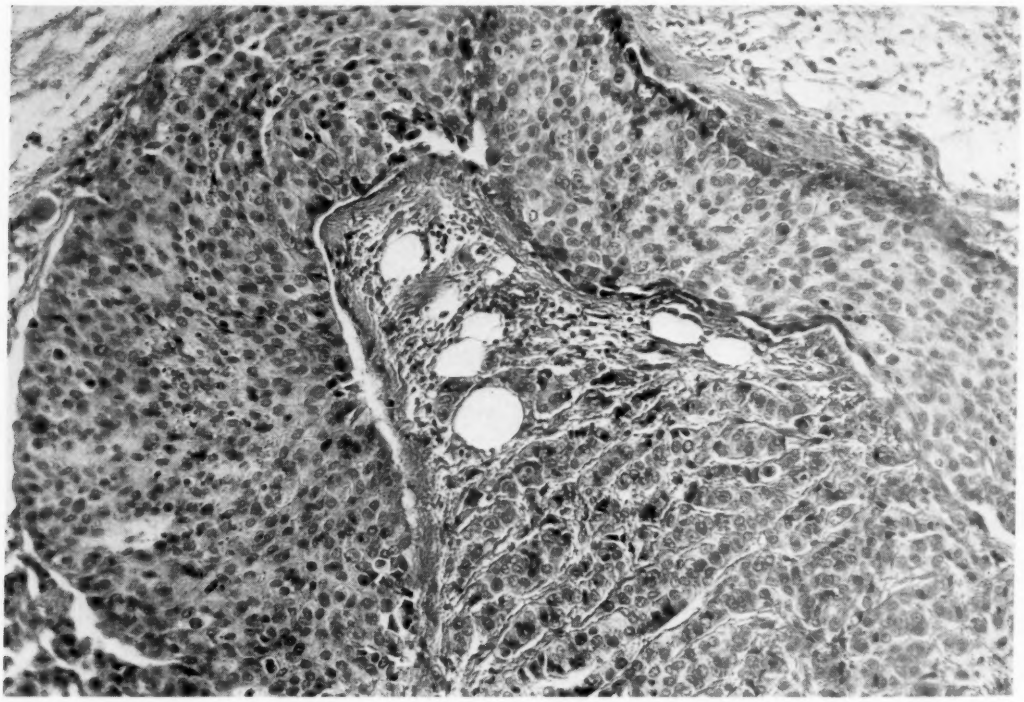

Fig. 8.—Photomicrograph demonstrating typical duct cell carcinoma in the same patient as shown in Fig. 7, 8 years later. This patient had continued to receive estrogenic hormone therapy in large amounts.

CASE REPORTS

CASE 1.—A 36-year-old housewife was referred by her family physician for a tumor in the left breast in March, 1936. The patient gave a history of having had a bilateral salpingo-ovariectomy 6 years previously for "pelvic inflammatory disease." For one year prior to admission she had received hormone therapy in large doses for "menopausal symptoms." Examination revealed both breasts to be enlarged, tense, tender, and nodular and a thickened area approximately 5 cm. in diameter was observed in the upper outer quadrant of the left breast in which dilated ducts or small cysts (0.5 to 1 cm. in diameter) were palpable. Examination of biopsy material from this area revealed cystic disease with dilated ducts, microscopic cysts, and marked proliferation of the duct epithelium and connective tissue stroma, as shown in Fig. 7. The patient was advised to discontinue hormone therapy.

The patient was not seen again until February, 1944, 8 years later at the age of 44 years, at which time she stated she had observed a tumor in the inner quadrant of the left breast one month previously. Examination revealed no evidence of pathology in the area

of breast from which the biopsyy had been taken 8 years earlier. However, a tumor approximately 3 cm. in diameter, which had the clinical appearance of carcinoma, was removed from the inner quadrant of the breast and immediate frozen section revealed duct cell carcinoma (Fig. 8). The patient stated that she had continued to receive estrogenic therapy following the biopsy in 1936. A radical mastectomy was performed; a total of 35 lymph nodes removed from the axilla were negative for metastases. The patient was last observed in 1955 at the age of 55 years at which time she was clinically free of the disease.

CASE 2.—A 44-year-old teacher was referred by her physician in July, 1935, for a discrete, firm mass in the upper outer quadrant of the right breast. Biopsy of the area revealed so-called "chronic cystic mastitis." Histologic examination of the specimen demonstrated marked proliferative changes of the duct epithelium; the small ducts contained apocrine epithelium and cellular debris (Fig. 9). The patient was observed at regular intervals for a period of one year and had no further involvement of either breast.

Three years later at the age of 47 years, the patient was again observed with painful nodularity throughout both breasts. She stated that she had been receiving 20,000 units of estrogenic hormone twice weekly for a period of one year following an abdominal hysterectomy for fibromyomata of the uterus. The patient was advised to discontinue all hormone therapy and was assured that the nodularity was benign.

The patient was again observed in November, 1944, 9 years after the initial biopsy of the benign lesion. Examination revealed a hard mass, approximately 4 cm. in diameter, involving the medial quadrant of the right breast with retraction of the skin over the mass. One hard lymph node was palpable in the axilla. Biopsy of the involved area revealed adenocarcinoma with extensive lymphocytic infiltration (Fig. 10). Radical mastectomy was performed; 3 of the 29 lymph nodes removed from the axilla contained metastases. The patient was given postoperative irradiation therapy but expired from generalized metastasis in 1952, 6 years after radical mastectomy was performed.

CASE 3.—An unmarried secretary, 36 years of age, was seen in March, 1937, with a nodular area in the upper outer quadrant of each breast. Examination revealed the patient had small breasts with a history of mastodynia over a period of 12 years. Nodular areas resembling dilated ducts and small cysts, 1 to 2 cm. in diameter, were present in the upper outer quadrant of each breast; there was definite thickening in the right breast beginning in the areolae and extending to the periphery. Biopsy of this area revealed marked proliferative changes in the epithelium of the ducts and acini, almost occluding the ducts (Fig. 11). A diagnosis of so-called "chronic cystic mastitis" was made. The patient continued to have pain in both breasts for a period of one year at which time she had an abdominal hysterectomy performed elsewhere for fibromyomata of the uterus. Following the hysterectomy the patient had no further discomfort in the breasts but received estrogenic hormone therapy by her family physician for "menopausal symptoms."

The patient was next observed in June, 1950, with a hard tumor, approximately 3 cm. in diameter, in the upper outer quadrant of the left breast; there was retraction of the skin over the tumor. The axillary lymph nodes were not clinically involved. Biopsy of the tumor revealed scirrhus carcinoma (Fig. 12). Radical mastectomy was performed and none of the 26 lymph nodes removed from the axilla was found to be involved by carcinoma. The patient was last seen in 1954 at which time she was clinically free of the disease.

CASE 4.—A housewife, 42 years of age, was referred by her physician in March, 1938, for a discrete tumor in the upper outer quadrant of the right breast. The patient had had 12 normal pregnancies the last of which had occurred 2 years previously. On examination, a well-differentiated, fluctuating tumor, approximately 6 cm. in diameter, was present; no other pathology was observed in either breast. There was a greenish-colored discharge from the nipple of the right breast. The patient's inability to undergo regular follow-up examinations because of distance made surgical removal of the cyst advisable. At operation, a thin-walled cyst and areas of nodular breast tissue adjacent to the cyst were excised. A diagnosis of cystic disease was made and histologic examination of tissue revealed marked

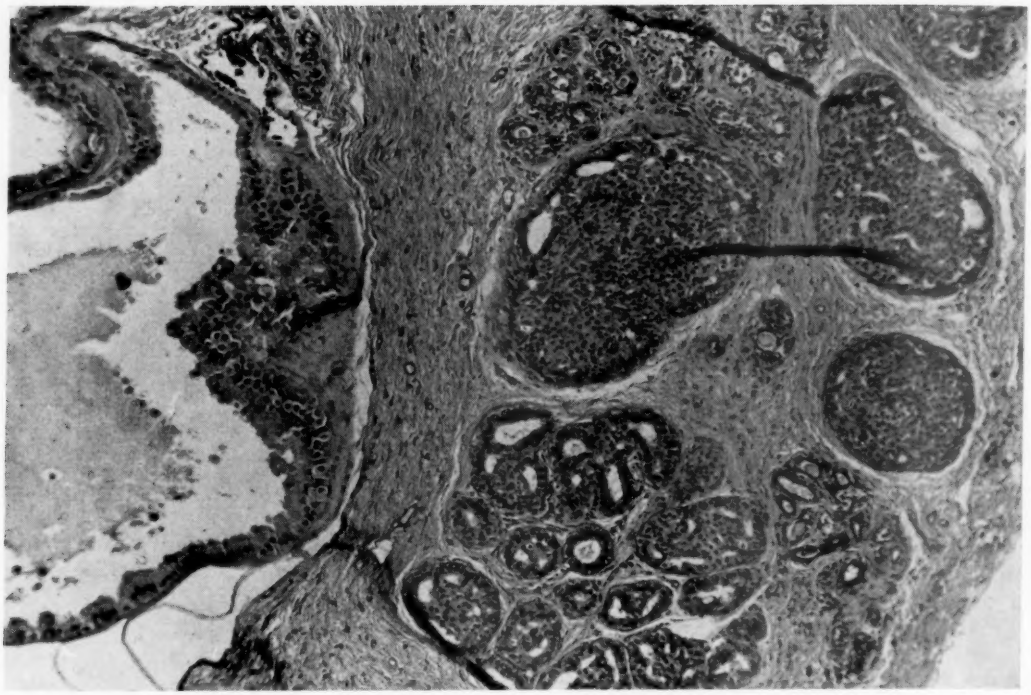

Fig. 9.—Photomicrograph of biopsy material from breast of 44-year-old patient with cystic disease which demonstrates aprocrine epithelium and small ducts filled with proliferative epithelial cells.

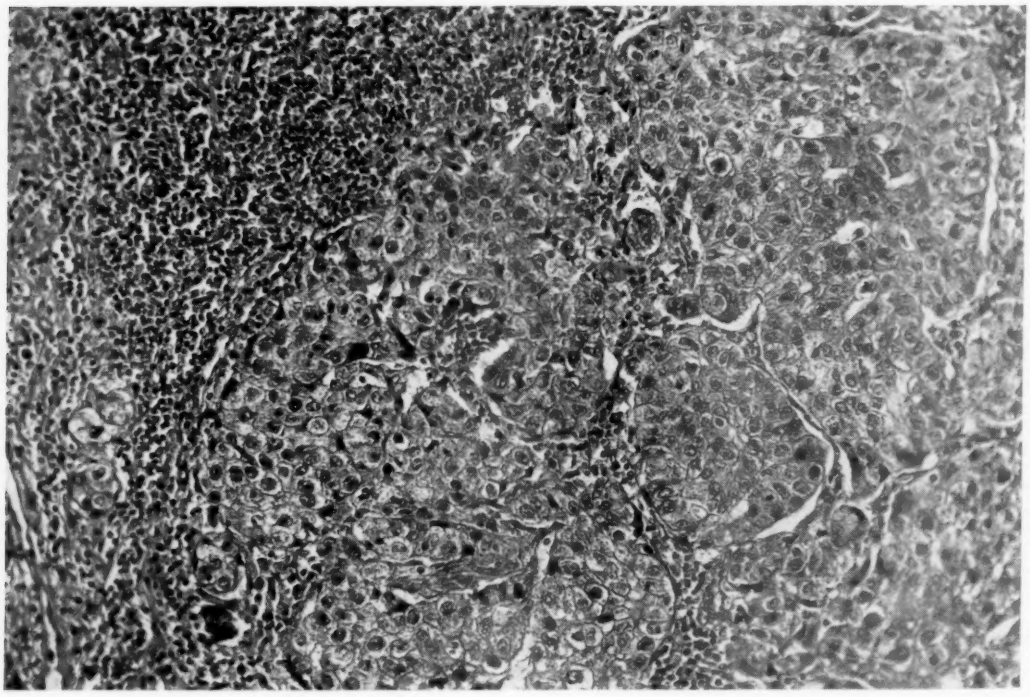

Fig. 10.—Photomicrograph of opposite breast of same patient as shown in Fig. 9, at the age of 54 years, which demonstrates adenocarcinoma with extensive lymphocytic infiltration.

Fig. 11.—Photomicrograph demonstrating marked epithelial proliferation almost filling dilated duct which has a thickened wall, in a 36-year-old patient.

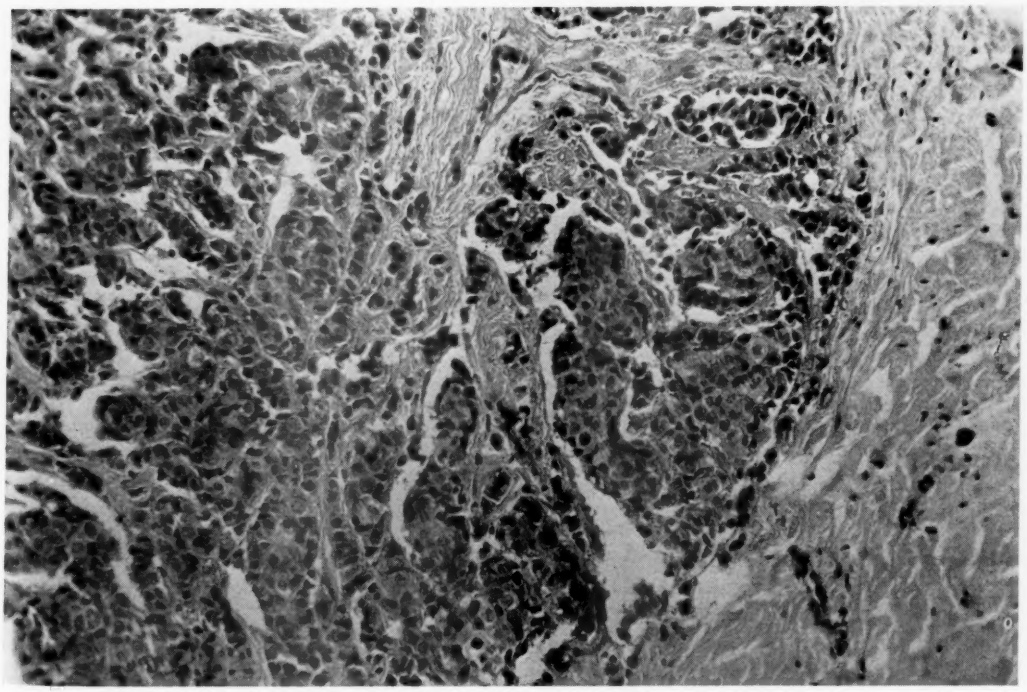

Fig. 12.—Photomicrograph demonstrating scirrhus carcinoma from opposite breast of same patient as shown in Fig. 11, 13 years later at the age of 49 years.

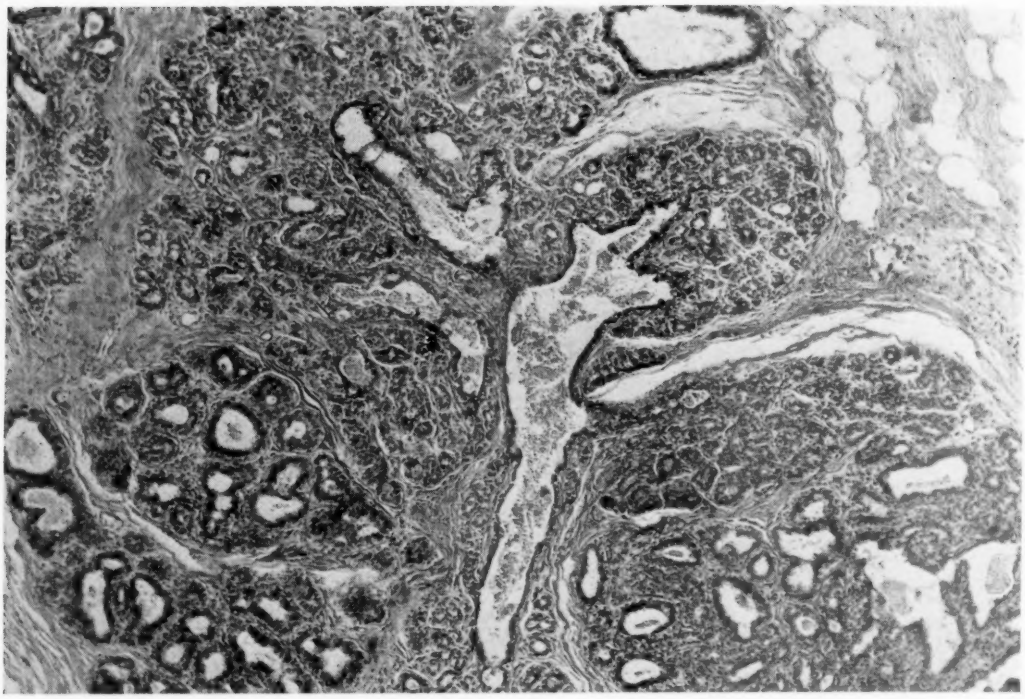

Fig. 13.—Photomicrograph of biopsy material from breast of patient 42 years of age with cystic disease which demonstrates marked epithelial proliferation and multiple small dilated ducts containing cellular debris. There was a greenish-colored discharge from the nipple.

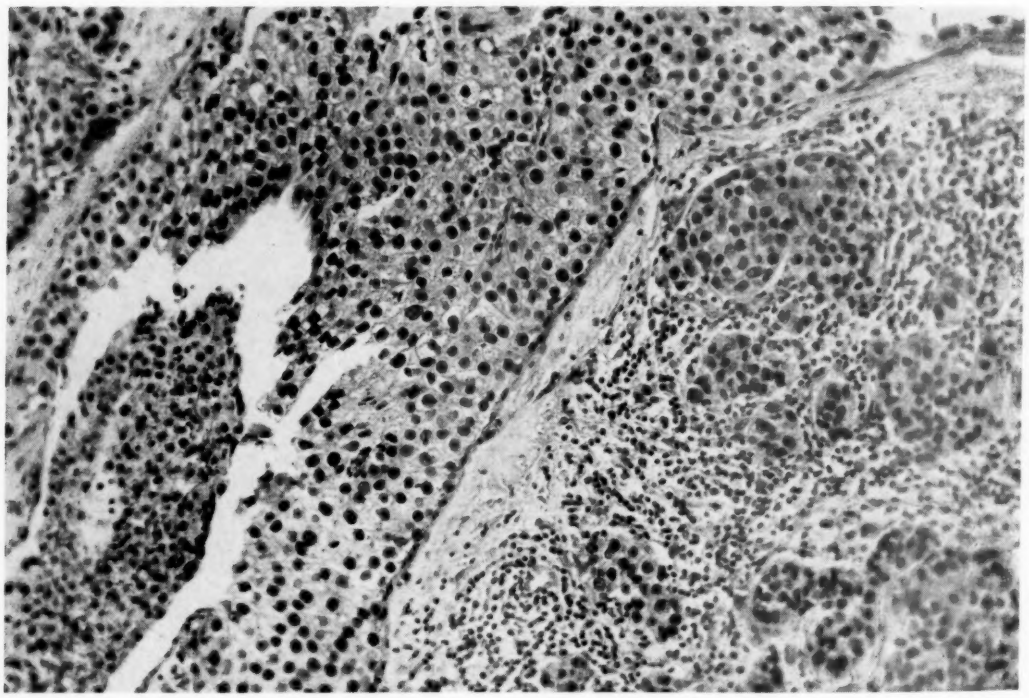

Fig. 14.—Photomicrograph demonstrating duct cell carcinoma in same patient as shown in Fig. 13, 12 years later, at the age of 54 years.

epithelial proliferation involving the duct epithelium; many of the small dilated ducts contained cellular debris (Fig. 13). The patient was next observed in 1944 following a vaginal hysterectomy performed elsewhere for uterine prolapse; on examination, her breasts were clinically normal.

Th patient was again observed in November, 1950, with a hard tumor in the left breast which measured approximately 4 cm. in diameter; there was retraction of the skin over the tumor. Two lymph nodes were palpable in the axilla. The opposite breast which had been previously involved with cystic disease was normal. The patient gave a history of having received estrogenic hormone therapy for a period of 2 years prior to admission. Biopsy of the tumor revealed duct cell carcinoma (Fig. 14). A radical mastectomy was performed; 7 of the 25 lymph nodes removed from the axilla contained metastases. The patient was given postoperative irradiation therapy and was clinically free of the disease when last observed in December, 1955.

A review of the histories of 452 patients with primary carcinoma observed during the same period that this series of patients with cystic disease of the breast was treated reveals that 4 patients had a history of a previous operation for a benign lesion of the breast. These 4 case histories were reviewed to determine the type of tumor and length of time which lapsed between its removal and the development of carcinoma. Pathologic slides of tissue removed could be obtained in only one of the 4 cases.

PATIENT 1.—This patient was observed at the age of 58 years with a duct cell carcinoma of the right breast. She gave a history of having had a benign tumor removed from the same breast 14 years previously. Correspondence with her physician revealed that a lump had been removed and a diagnosis of chronic cystic mastitis had been made. No pathologic slides were available. The scar from the previous operation was located on the medial quadrant of the right breast and the carcinoma was located in the upper outer quadrant of the same breast.

PATIENT 2.—A 49-year-old housewife had duct cell carcinoma involving the medial quadrant of the right breast. There was a scar 4 cm. in length in the upper outer quadrant of the same breast. The patient stated that a cyst had been removed under local anesthesia in her physician's office 12 years previously and no pathologic examination of the tissue had been made.

PATIENT 3.—A 46-year-old unmarried teacher was treated for duct cell carcinoma of the right breast in 1940. She stated that a tumor had been removed from her left breast by her family physician 20 years previously. There was a small scar in the upper outer quadrant of the left breast which measured 5 cm. in length. Her physician was deceased; pathologic slides were obtained from the hospital where the operation had been performed and a diagnosis of adenofibroma was established.

PATIENT 4.—The 52-year-old wife of a medical missionary was found to have duct cell carcinoma of the right breast. The patient stated that 18 years previously a tumor had been removed from the left breast under local anesthesia by a physician in the missionary service in India. No histologic examination of tissue removed had been made, but the patient had been advised that, grossly, the specimen contained small cysts. The patient stated that the wound had drained for a period of several months following the operative procedure.

TREATMENT

The most significant question concerning treatment of cystic disease of the breast is: What advice is the surgeon to give patients with a painful, nodular breast and what source of authority will provide him with an intelligent answer

for these patients? It has been my practice, after a clinical and pathologic diagnosis is established, to assure the patient unequivocally that she is no more likely to develop carcinoma of the breast than a patient of comparable age without cystic disease.

Patients in a younger stage of menstrual life with small granular or nodular breasts which are painful, apparently resulting from excessive estrogenic stimulation, certainly do not respond to estrogenic hormone therapy. Androgen therapy has not proved beneficial in these cases due to side effects which most patients develop when androgens are given in sufficient quantities to relieve symptoms. Progesterone in oil, administered in 20 mg. doses twice weekly for 2 weeks before menstruation, gives some symptomatic relief.

Aspiration therapy for discrete cysts of the breast has been used by a number of surgeons with good results[20, 25, 27]; the aspiration should be performed only by surgeons qualified to perform a radical mastectomy when carcinoma is encountered. Since 1933, I have treated certain patients with discrete cysts of the breast by aspiration of the cyst contents with satisfactory results; however, this method of therapy is not recommended unless the patient agrees to return for follow-up examinations at regular intervals and this group of patients have cooperated well when this modality of therapy was used. The patient is informed in the beginning that if any of the following conditions develop and persist, the area is to be excised promptly and histologic examination will be made of tissue removed: (1) when aspiration produces a bloody fluid or if the fluid returns immediately following a second aspiration; (2) if the lump in the breast does not completely disappear following aspiration; or (3) if aspiration does not yield fluid.

The technique used for aspiration of a cyst in the breast consists of making an intradermal skin wheal over the most prominent area of the tumor with a 26-gauge needle, using 1 per cent procaine solution. The tumor is stablized with the thumb and fingers of one hand and a 20-gauge needle with a short bevel attached to a 10 or 20 c.c. syringe is inserted into the mass. Care is exercised to stop the needle at its entrance into the cyst to prevent trauma which could result in bleeding (Fig. 15). In patients with large breasts in which the cyst is deeply located, a lumbar puncture needle with a stilet is preferable to a standard hypodermic needle. After all fluid has been aspirated from the cyst by exerting pressure over it with the thumb and fingers of the opposite hand, a pressure dressing, using elastoplast, is applied which serves to obliterate the space especially when large cysts are aspirated. The pressure dressing is changed at 4- or 5-day intervals for a period of 2 to 3 weeks.

One hundred sixty-seven patients with discrete cysts of the breast observed over a period of 5 to 18 years were treated by aspiration therapy (Table IV); 15 of these patients required 2 aspirations. In 19 patients, a second cyst formed in another area of the same breast and in 13 patients a cyst developed in the opposite breast later. These new cysts developed after periods from a few months to as long as 16 years following aspiration of the first cyst. They were all successfully treated by aspiration therapy.

TABLE IV. RESULTS OF TREATMENT BY ASPIRATION OF 167 PATIENTS WITH CYSTIC DISEASE OF THE BREAST

PERIOD FOLLOWED (YEARS)	PATIENTS IN WHOM FLUID WAS OBTAINED BY INITIAL ASPIRATION	PATIENTS IN WHOM CYST REFILLED FOLLOWING 2 OR MORE ASPIRATIONS	PATIENTS IN WHOM RESIDUAL MASS WAS PRESENT FOLLOWING ASPIRATION	PATIENTS IN WHOM NEW CYST FORMED IN SAME BREAST	PATIENTS IN WHOM CYST FORMED IN OPPOSITE BREAST	PATIENTS FOLLOWED
5- 9	58	5	3	5	4	54
9-13	63	8	2	8	5	59
13-18	46	3	2	6	4	37
Total	167	16	7	19	13	150

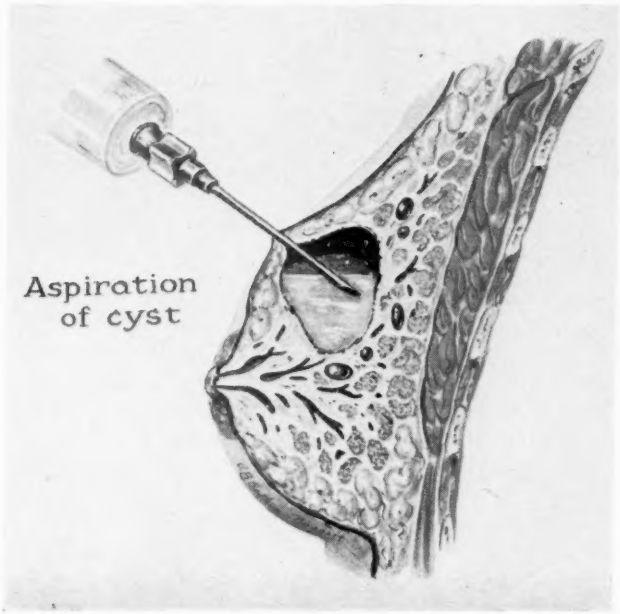

Fig. 15.—Technique used for aspiration of discrete cyst of the breast which is utilized as a diagnostic and therapeutic procedure.

Seven patients had a residual mass after dry aspiration of what appeared, clinically, to be a discrete cyst. These patients had surgical excision of the tumor. In 2 patients a soft lipoma was found. In 2 other patients with large breasts in whom a segment of breast tissue was involved which simulated a discrete cyst, biopsy material revealed multiple dilated ducts with proliferated epithelium and microcysts. In 2 patients, 26 and 28 years of age, who had tumors approximately 8 and 10 cm. in diameter, respectively, no fluid was obtained on aspiration. The tumors were excised in both patients who had large breasts, and on microscopic examination both were found to be fibroadenoma. The seventh patient in whom a dry aspiration was carried out was 33 years of age and had a localized tumor that varied in size during each menstrual cycle. Histologic examination of biopsy material obtained by surgical excision revealed adenosis.

Aspiration can be safely used as a diagnostic and therapeutic measure for discrete cysts and has proved successful in this group of patients. It is more economical for the patient and, if there is any doubt about residual tumor after aspiration, surgical excision is carried out. Carcinoma was not encountered in any patient in this series on whom aspiration biopsy was performed (Table V).

TABLE V. PATHOLOGY OF RESIDUAL MASS FOLLOWING ASPIRATION OF BREAST CYSTS IN 7 PATIENTS

DIAGNOSIS	NUMBER OF PATIENTS
Lipoma	2
Multiple small cysts	2
Fibroadenoma	2
Adenosis	1
Total	7

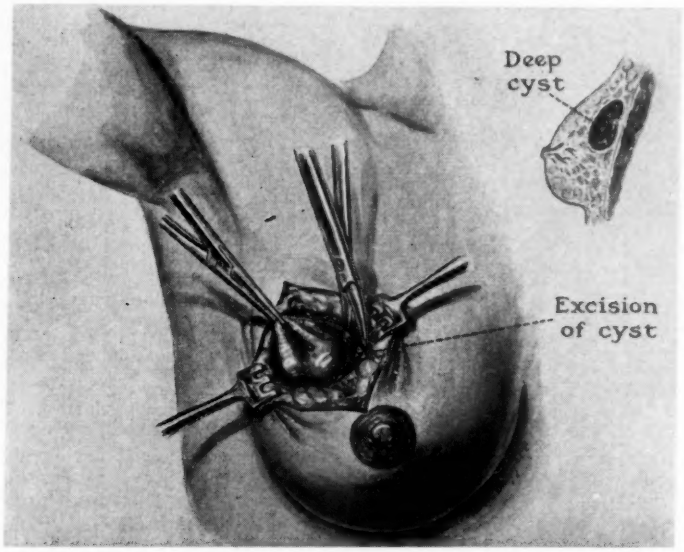

Fig. 16.—Technique used for surgical excision of a discrete cyst of the breast or segment of cystic disease. A radial incision begins at the areolae and extends to the periphery. The cyst or segment of involved tissue is excised using meticulous hemostasis. The wound is carefully explored for additional tumors and closed with fine 4-0 interrupted cotton sutures eliminating all dead space. The skin is closed with mattress sutures of silk. No drain is used. A pressure dressing is applied using elastoplast.

In patients with localized areas of cystic disease and those with discrete cysts who will not agree to regular inspection following aspiration therapy, surgical excision of the involved area is performed. A radial incision is begun at the areolae and extended to the periphery of the breast over the most prominent area involved (Fig. 16). If there is a discrete cyst present, its walls are caught with a hemostat and it is dissected out with a scalpel or dissecting scissors; all small vessels are clamped to maintain careful hemostasis which permits detection of any circumscribed or hard tumors which could represent carcinoma. All bleeding points are carefully ligated with 4-0 cotton sutures or electrocoagulation is used.

If a discrete cyst is present it is opened at the operating table and any thickened area of the wall is sectioned. In most instances breast cancer can be diagnosed by the surgeon at the operating table and careful frozen section in the laboratory only serves to confirm the diagnosis. If carcinoma is found, the wound is closed and the patient is prepared for radical mastectomy,[19] otherwise, the wound is carefully closed with interrupted 4-0 cotton sutures eliminating all dead space. The skin is closed with mattress sutures of silk; no drains are used. A pressure dressing is applied using elastoplast. In a rare case, following removal of a considerable amount of breast tissue, serum may collect in the wound and is removed by aspiration.

The surgeon who manages diseases of the mammary gland encounters some few patients, usually past the age of 40 years, with large breasts in whom one or both breasts have no definite thickened areas or evidence of localized tumor formation but which are riddled with cysts too small to be eradicated by aspiration. Examination of biopsy material is not deemed necessary in these cases and certainly simple mastectomy is not indicated. Such a condition regresses following menopause and, until that period occurs, the treatment I recommend is reassurance and regular examination. The anxiety associated with cystic disease of the breast is frequently the most prevalent feature and when this is relieved these patients are no longer greatly concerned with their symptoms.

In several instances patients have been encountered who had had benign tumors removed elsewhere through a transverse incision, either in the areolae or between the areolae and periphery of the breast. Such an incision severs and ligates the duct system and separates the ducts from their lobules in the breast tissue peripheral to the scar. These patients develop retention cysts in the mammary tissue peripheral to the transverse scar. The use of a radial incision does not produce this complication.

The results of treatment of 314 patients with either a discrete cyst or localized cystic disease of the breast who were followed from 5 to 18 years demonstrate that 311 of the patients had excision of a discrete cyst or excision of a localized area of breast tissue and in only 3 patients were simple mastectomies performed (Table VI). These 3 patients had severe mastodynia and there was history of breast cancer in more than 2 members of their immediate

TABLE VI. RESULTS OF TREATMENT OF 314 PATIENTS WITH CYSTIC DISEASE OF THE BREAST BY SURGICAL EXCISION

PERIOD FOLLOWED (YEARS)	PATIENTS WHO HAD EXCISION OF INVOLVED AREA OF BREAST	PATIENTS WHO HAD SIMPLE MASTECTOMY	PATIENTS IN WHOM NEW CYST DEVELOPED IN SAME BREAST	PATIENTS IN WHOM CYST DEVELOPED IN OPPOSITE BREAST	TOTAL NUMBER OF PATIENTS FOLLOWED
5- 9	145	1	7	7	134
9-13	108	1	8	6	96
13-18	61	1	4	3	51
Total	**314**	**3**	**19**	**16**	**281**

families. Nineteen of the 311 patients treated by surgical excision developed new cysts in another area of the same breast and 16 developed a cyst in the opposite breast at a later date. All 35 of these latter patients were successfully treated with aspiration therapy.

SUMMARY AND CONCLUSIONS

The vast amount of literature dealing with the extensive terminology, etiology, precancerous nature, and treatment of cystic disease of the breast, which is the most frequent abnormal condition encountered in the management of diseases of the mammary gland, has caused confusion in the minds of many concerning this benign problem. Early investigators held the view that cystic disease was not neoplastic in origin but resulted from an inflammatory reaction; hence, the term "chronic cystic mastitis" was widely adopted and has probably been the greatest handicap to an understanding of the disease because of the assumption that it was inflammatory in origin.

This report includes the clinical histories, operative findings, pathologic reports, treatment administered, and follow-up examinations on 90 per cent of a series of 484 private patients. The study was undertaken to determine the results of conservative therapy administered in cystic disease of the breast and to present any possible clues to its etiology, hormone influences which may affect the process, and the relation of cystic disease and breast cancer.

Extensive research has demonstrated that estrogenic stimulation which is continued over a period of time in ovariectomized mice will produce proliferation and metaplasia of the mammary duct epithelium with dilatation of the ducts and acini; microcysts will form. This histologic picture in mice is comparable to cystic disease in the human except that in mice the entire breast is affected whereas in the human the disease is usually localized to one segment of the breast. Kier and associates[21] may have thrown a beam of light upon the hormonal influence when, in 15 consecutive cases, they discovered associated abnormal changes in the endometrium biopsied simultaneously with the breast, indicating the possible lack of an estrogenic antagonist rather than excessive estrogenic stimulation.

It seems feasible, if excessive estrogenic stimulation is the causative factor in the production of metaplasia and proliferative changes in the duct epithelium and stroma, that the age of the patient and the length of time the stimulus is effected may have a bearing on benign and malignant lesions of the breast. For example, if such a stimulus is present in a patient in her twenties, a fibroadenoma would result; in the same individual between the age of 35 and 45 years, the stimulus would result in cystic disease and possibly, if such a stimulus persisted after the meonpause, malignancy would result. This, of course, is purely speculative.

The extensive use of estrogens in all forms for so-called "menopausal symptoms" in patients with nervous phenomena certainly should increase the incidence of cystic disease and carcinoma of the breast if the theory could be proved that estrogenic stimulation is related to malignancy of the breast. Since

1940, at least 60 per cent of the patients on whom I have made a diagnosis of cystic disease or carcinoma of the breast had histories of having had estrogenic therapy in varying amounts over a period of months to several years. A number of these patients who were past the menopause stated that their breasts had been free of symptoms until the administration of estrogen therapy after which their breasts became tender, tense, painful, firm, and nodular.

It has been established by Goldberg and associates[14] that approximately one of every 20 women in the state of New York develops carcinoma of the breast in a lifetime. A careful follow-up of this series of 484 patients with cystic disease for a period of 5 to 18 years disclosed that only 4 developed carcinoma of the breast. Of 452 patients with primary carcinoma of the breast who were treated during the same period, 4 had previously undergone surgery elsewhere for benign lesions of the breast.

For the reason that some authors believe cystic disease of the breast to be a precancerous lesion and recommend simple mastectomy for its treatment, the management of this disease proposes 2 important questions for the clinical surgeon: What advice is he to give patients who consult him with painful, nodular breasts, and what source of authority will provide him with an intelligent answer for such patients? It is my practice, when a diagnosis of cystic disease is established, to assure the patient that there is no more likelihood of carcinoma developing in her breast than in that of any patient of comparable age without cystic disease and that simple mastectomy is not necessary except in rare cases. Patients in the earlier period of menstrual life with small, nodular, painful breasts are administered progesterone in oil, 20 mg. twice weekly for 2 weeks before menstruation, which gives some symptomatic relief.

Since 1933 I have used aspiration therapy for discrete cysts of the breast, provided the patient agrees to return at regular intervals for further evaluation. This procedure is more economical for the patient and in only 7 of the 167 patients with discrete lumps treated by aspiration was there a residual mass following dry aspiration. These patients had surgical excision of the tumors, which were benign in all 7.

Patients with discrete cysts are advised that if aspiration produces bloody fluid, if the lump does not completely disappear following aspiration, if fluid is not obtained, or in the event that the lump returns after a second aspiration, the involved area of breast will be excised for histologic examination. Regular follow-up examinations of patients in whom aspiration was performed demonstrated that carcinoma was not overlooked in any instance.

Of 314 patients who had either a discrete cyst or an area of cystic disease localized to one segment of the breast, 311 had surgical excision of the involved area. Three patients had simple mastectomy due to severe mastodynia and the fact that the involved breasts were riddled with small cysts; in all 3 cases there was history of breast cancer in several members of the immediate family.

Sixty-seven patients, treated either with aspiration therapy or surgical excision of a discrete cyst or segment of breast affected with cystic disease,

developed a second cyst in the same or opposite breast after a period of several months to 16 years. The new cysts were successfully treated by aspiration therapy.

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PAROTID TUMORS

A 10- to 15-Year Follow-up

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THIS is a 10- to 15-year follow-up of a series of 28 patients with radical parotidectomies. A review of the American literature has failed to reveal a similar evaluation. This study was undertaken in 1943 when the treatment of parotid tumors had no standardization whatever. Simple enucleation was practiced extensively violating all the precepts of good tumor surgery and resulting in frequent recurrence and a high incidence of seventh nerve damage. Dr. Vilray P. Blair and his associates[2] of St. Louis and Dr. Donald Trueblood[9] of Seattle were notable exceptions. They advocated total removal of the parotid gland and tumor with preservation of the facial nerve. The purpose of this paper is to present the results of consecutive patients operated upon for parotid tumor in a single standardized manner by one surgeon in the years 1943 through 1947. This should reduce the variability of results to a minimum. Our experience with the technique to be described is based upon 78 radical parotidectomies done since 1943. Twenty-eight of these have been followed from 10 to 15 years and are the patients to be presented.

Dr. John C. Warren[10] of Boston performed the first parotidectomy in 1804. His exact procedure is unknown. Corwardine[4] in 1907 performed the first recorded complete excision of the parotid gland with preservation of the facial nerve.

Since Virchow in 1863 described enchondromas of the parotid, pathologists have had many classifications for parotid tumors. In general, they confuse rather than clarify the problem. It is impossible through microscopic study of their structure to be dogmatic about their clinical behavior. It is probably permissible for clinical purposes to consider them under 2 general headings, mixed tumors and frank carcinomas. The mixed tumors usually follow a benign course, but many behave as carcinomas of low malignancy. Late in the course of the disease, cervical lymph-node metastasis and extensive local invasion with destruction of tissue may occur. Certain of the carcinomas may present morphologic and clinical characteristics not far removed from the clinically benign mixed tumors. This paper will not discuss the histology of parotid tumors as this phase has been extensively covered in the literature.

The reported recurrence rate for mixed tumor in the literature is 25 to 50 per cent. McFarland[7] reported a recurrence rate of 25 per cent with the

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average time of recurrence being 7 years after the first excision. He states that the recurrence rate for malignancies is higher and that they recur earlier than mixed tumors. Reporting the Mayo Clinic series in 1951, Kirklin[6] stated that one-third of the mixed tumors recurred and that one-half to two-thirds of the malignant tumors recurred. The patients in their series were operated upon by various surgeons using different procedures and the patients were followed for varying lengths of time. Thus, the evaluation of results is obviously difficult. It is evident that the recurrence rate in any given series increases directly with the period of observation.

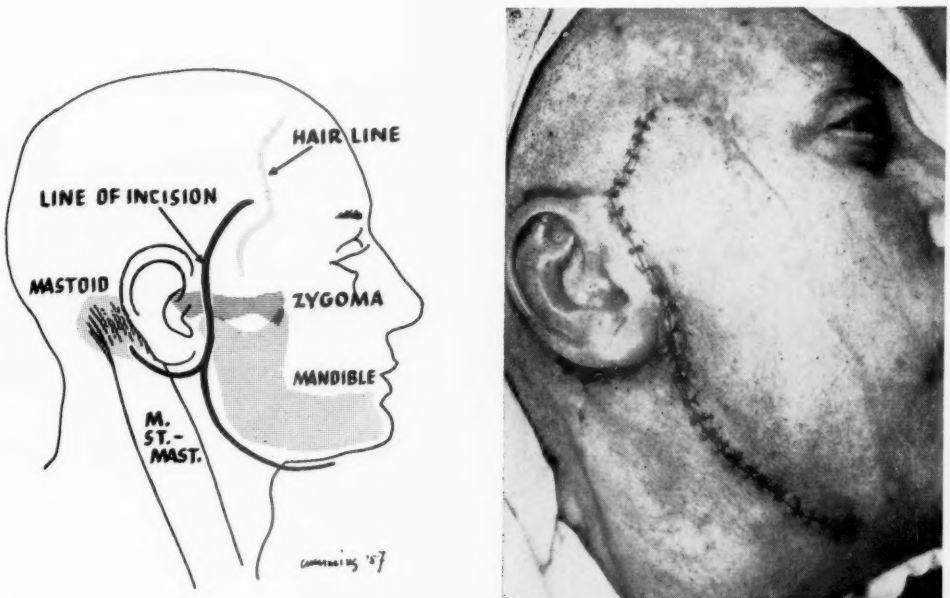
PROCEDURE

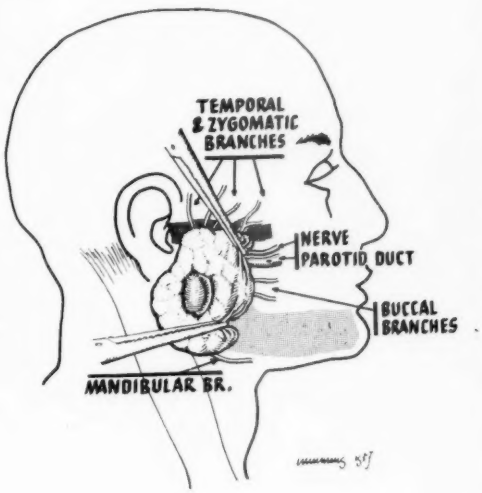
The patients were all informed of the procedure to be done. This included the warning of probable temporary facial paralysis of varying degree and possible sacrifice of the nerve in case of malignant involvement resulting in permanent nerve injury. Preoperative preparation included shaving the hair approximately 2 inches above the level of the ear anteriorly and extending posteriorly to the midline of the neck. The operative procedure was identical in all cases. The incision is positioned on the skin 1.0 to 1.5 cm. below the inferior ramus of the mandible, at least as far forward as the mid-portion, and is brought just anterior to the ear, then forward immediately above the hairline (Fig. 1). The portion above the hairline is hidden postoperatively and at the time of operation allows a very adequate anterior flap to be developed. A posterior component is carried back just below the lobe of the ear and over the mastoid. The flaps are turned up in all directions as full-thickness flaps, thus allowing removal of the fat and platysma overlying the gland. Identification of the branches of the seventh nerve is begun at the periphery of the field outside parotid tissue and developed toward the main trunk of the nerve. The mandibular branch of the facial nerve is located most easily at the site where it crosses the anterior facial vein and artery (Fig. 2). The temporal and zygomatic branches will be seen over or immediately above the zygomatic bone. There is usually a large branch which accompanies the parotid duct one finger-breadth below the zygoma. The duct can be easily identified if it is looked for just before entering the buccinator muscle. The peripheral identification of the seventh nerve branches and the dissection of the parotid posteriorly have the advantage of a more complete block of tissue being developed before the tumor area is approached. Most of the tumors are nearer the main nerve trunk than the periphery. We are able to reflect the superficial portion of the gland along the plane of these nerve branches as an intact block along with the tumor, which usually is situated in this superficial area. The deep portion of the gland is removed by freeing the nerve then working between and around the branches. Occasionally it can be worked out intact but more often it is divided. After complete removal of all parotid tissue, the area is generously irrigated with warm saline. A Penrose drain is used below the ear and the subcutaneous and skin margins are approximated with 4-0 silk sutures. An adequate firmly applied pressure dressing is considered a very important and essential step.

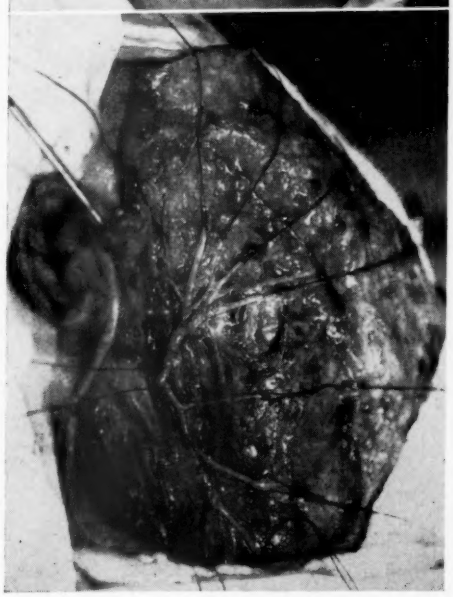
A routine biopsy is not done. It is our feeling that the farther we stay away from the tumor in our dissection the better. Thus, we avoid contaminating

the surrounding parotid tissue with tumor, which is our goal. At operation a broken soft edge or a ruptured cyst in the parotid tumor is a highly undesirable event to be avoided at all costs. This may result in the very rare case of a stone or a stone with inflammatory tissue around it being removed in a radical fashion. While this is undesirable, it will occur so rarely that we

A. Fig. 1. *B.*







A. Fig. 2. *B.*

Fig. 1.—*A*, Schematic illustration of the location and extent of the skin incision. *B*, Photograph of patient at completion of surgery. Note the extent of the incision.

Fig. 2.—*A*, Schematic illustration of the relationships of the facial nerve and the parotid gland. *B*, Photograph of the distribution of the facial nerve following radical parotidectomy.

TABLE I. TWENTY-EIGHT CASES OF RADICAL PAROTIDECTOMY FOLLOWED 10 TO 15 YEARS

	NO.	PREVIOUS OPERATIONS	NUMBER PREVIOUS OPERATIONS	RECURRENCE AFTER SURGERY	DEAD FROM DISEASE	DEAD FROM OTHER CAUSES	LOST TO FOLLOW-UP	X-RAY BEFORE OR AFTER SURGERY	INJURED SEVENTH NERVE	ALIVE AND WELL WITHOUT EVIDENCE OF DISEASE
Carcinomas	12	6 1-4 times	6	1	1 10 mo.	2 Both 7½ yr. after surgery 1 coronary 1 cerebral accident No evidence of carcinoma	1	5 3 dead, 2 alive and well	3 All intentionally sacrificed	8
Mixed tumors	16 1 Warthin's tumor	5	11	2	0	0	0	2	0 1 mandibular branch	16

do not consider it seriously. It has occurred only one time in 78 radical parotidectomies and is considered a small penalty for avoiding spillage or the seeding of tumor cells occurring with biopsies.

CLINICAL APPRAISAL

There were 28 consecutive cases operated upon over a 5-year period, 1943 through 1947. There has been one case lost to follow-up. The remaining cases have all been followed over 10 years; the longest follow-up is now over 15 years. Malignancy was found in 12 cases and 16 cases were benign (Table I and Fig. 3).

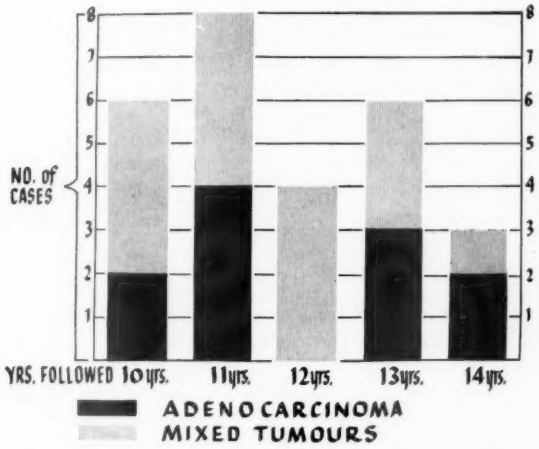


Fig. 3.—The duration and distribution of the follow-up on 28 cases of radical parotidectomies.

It is noted from our observations that of the 12 carcinomas treated by surgery we have only one recurrence which resulted in the patient's death 10 months later. This was a very far-advanced carcinoma first noted in 1931 which had grown to huge proportions. This patient had been treated elsewhere with x-ray on 3 occasions, the first in 1937. This case should never have been submitted to surgery (Fig. 4). There were 2 mixed tumors of the 16 operated upon that recurred 4 and 5 years, respectively, after the initial surgery. Both recurred in the skin along the scar of the incision. One of these was a 2 mm. millet seed. They have gone now for 5 and 6 years, respectively, without evidence of further recurrence. It is to be noted, therefore, on a long-term follow-up that the carcinomas and the mixed tumors did not behave very differently. Slaughter[8] found that 12 of 55 (20 per cent) malignant tumors originated in previously benign tumors. Beahrs and associates[1] from the Mayo Clinic in reviewing a series of 178 tumors which had been reported as malignant found that 29 (16 per cent) evidenced the association of benign mixed tumors and frank carcinoma compatible with carcinomatous transformation of mixed tumor.

The patient with the Warthin's tumor (papillary cyst adenolymphomatosum) was included with the mixed tumors. We believe they should be treated precisely as the mixed tumor. At surgery there is no way to differentiate the mixed tumor and Warthin's tumor accurately except histologically. The

recurrence rate is higher in the Warthin's tumor than in the mixed parotid tumor. "There are very few figures available on recurrence rates of papillary cystadenoma lymphomatosum based on long-term follow-up. In the 44 patients treated at Memorial Hospital, there were six recurrences from surgical procedures on 49 tumors; hence it appears that the rate of recurrence is somewhat higher than expected in mixed tumors, although the total number of cases for this determination is too limited to be final."[5]

All of the patients reported here developed some degree of temporary facial paralysis following operation. This varied from a few days to 8 months for complete recovery where the nerve was not permanently damaged. It was observed that where dissection was especially laborious and difficult, because of the size or fixation of the tumor, temporary paralysis of the seventh nerve was increased. Three of the carcinomas directly invaded the facial nerve trunk so that it was impossible to remove the tumor and spare the nerve. In these patients it is often necessary to take considerable lengths of the nerve, making

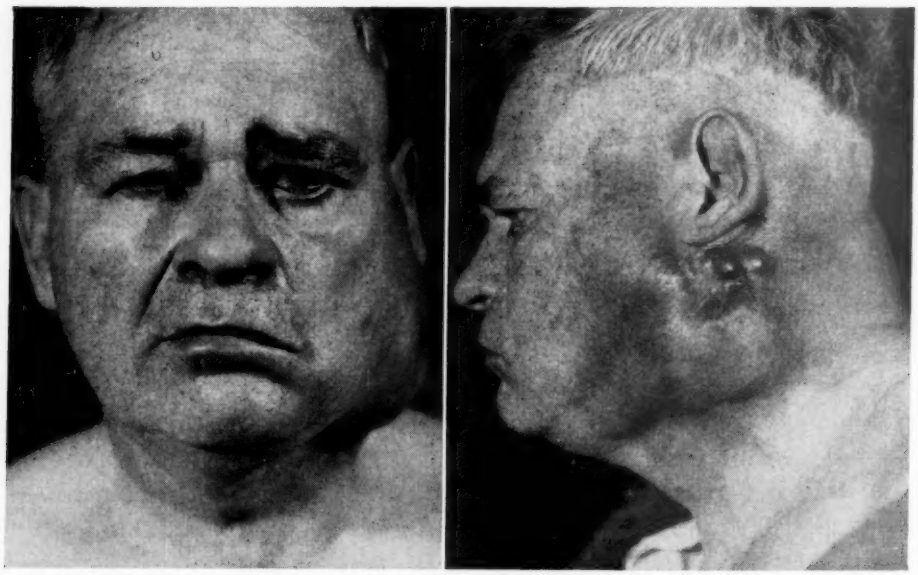


Fig. 4.—Photograph of a case of adenocarcinoma of the parotid. This the onset of disease in this patient was in 1931. He had had 3 attempts at control by irradiation. As can be noted the disease is extensive.

any approximation out of the question. Conley[3] has recently described his technique and results following graft repairs of the seventh nerve in just such cases. We have had no experience in the management or repair in this problem. In our operative experience with these tumors it has constantly been a source of amazement to note the extreme variations in the size, position, general contour, and number of branches of the facial nerve. Nothing is standardized about it except the fact that there are numerous small filaments which anastomose between the larger branches. This unquestionably saves surgeons much embarrassment. The surgeon must constantly be on the alert because of these variations and the small size of the structures he is dissecting.

The great auricular nerve is cut in the radical operation. This should be remembered postoperatively, for some patients develop a neuroma often quite evident to them. They should be reassured this does not represent a recurrent tumor mass.

The full-thickness skin flaps turned up in our operative procedure are extensive but assure excellent exposure. The lack of an unsightly scar will often depend upon how neatly these flaps heal to the underlying tissue. A collection of serum beneath the flaps is undesirable and will be prevented by the application of a snug, well-fitting dressing using sponge rubber for uniform pressure.

Salivary fistula has not been a problem to us. It is desirable to leave as little duct as possible as the duct remnant will occasionally become the site of a chronic low-grade infection months after surgery. The patient will be able with pressure to express purulent matter into the mouth.

The Frei syndrome is a possible annoying postoperative sequelae. It usually appears within 2 years after surgery and consists of flushing and/or sweating in the area of the skin flaps developed at the time of surgery. The reaction occurs during the meal or shortly afterward. The true mechanism of this syndrome is not certain; however, it is felt that the possible mechanism may result from stimulation of the tongue with reflections of this stimulation through the glossopharyngeal nerve to the otic ganglion and to the auriculotemporal nerve. The auriculotemporal nerve is a sensory nerve to the skin in the region of the parotid. The divided branches of this nerve then anastomose to the distal branches of the sympathetic system which supply the skin and which were severed by the flap. Thus, by an injured system, sweating occurs.

DISCUSSION

We believe that no patient in good health should ever have enucleation of any part of the parotid gland for a parotid tumor. It is necessary to remove all portions of the parotid gland for a parotid tumor whether it is a mixed tumor or a carcinoma. We believe that rarely should a facial nerve be injured permanently in a radical operation for a mixed tumor (Figs. 5 and 6). It is felt that the radical exposure of the nerve will be followed by fewer injuries than occur with the procedures of excision or enucleation which are done without nerve visualization. The facial nerve should be injured in a carcinoma only when the nerve trunk or branch is invaded directly by carcinoma. These facts constitute our observations and bases for treatment of parotid tumors. It is our belief based upon our 10- to 15- year observations that both the carcinoma and mixed tumor of the parotid are ordinarily not vicious tumors if they are seen relatively early in their course and treated radically. To predict that a mixed tumor is not multicentric in origin and will not at some time present malignant characteristics is impossible. In good hands a radical parotidectomy does not leave either an unsightly face or a paralyzed one. Little argument remains that radical surgery is the mode of treatment. Radical surgery would have spared one-half of our patients with carcinoma and one-third of those with mixed tumors from 1 to 4 operations prior to the

time we initially saw them. We attribute our low recurrence rate to an unrelenting adherence to these principles. A wide exposure obtained by use of an adequate skin incision exposing the whole gland assures maximum ability to do a thorough parotidectomy and preserve intact the seventh nerve.

Fig. 5.

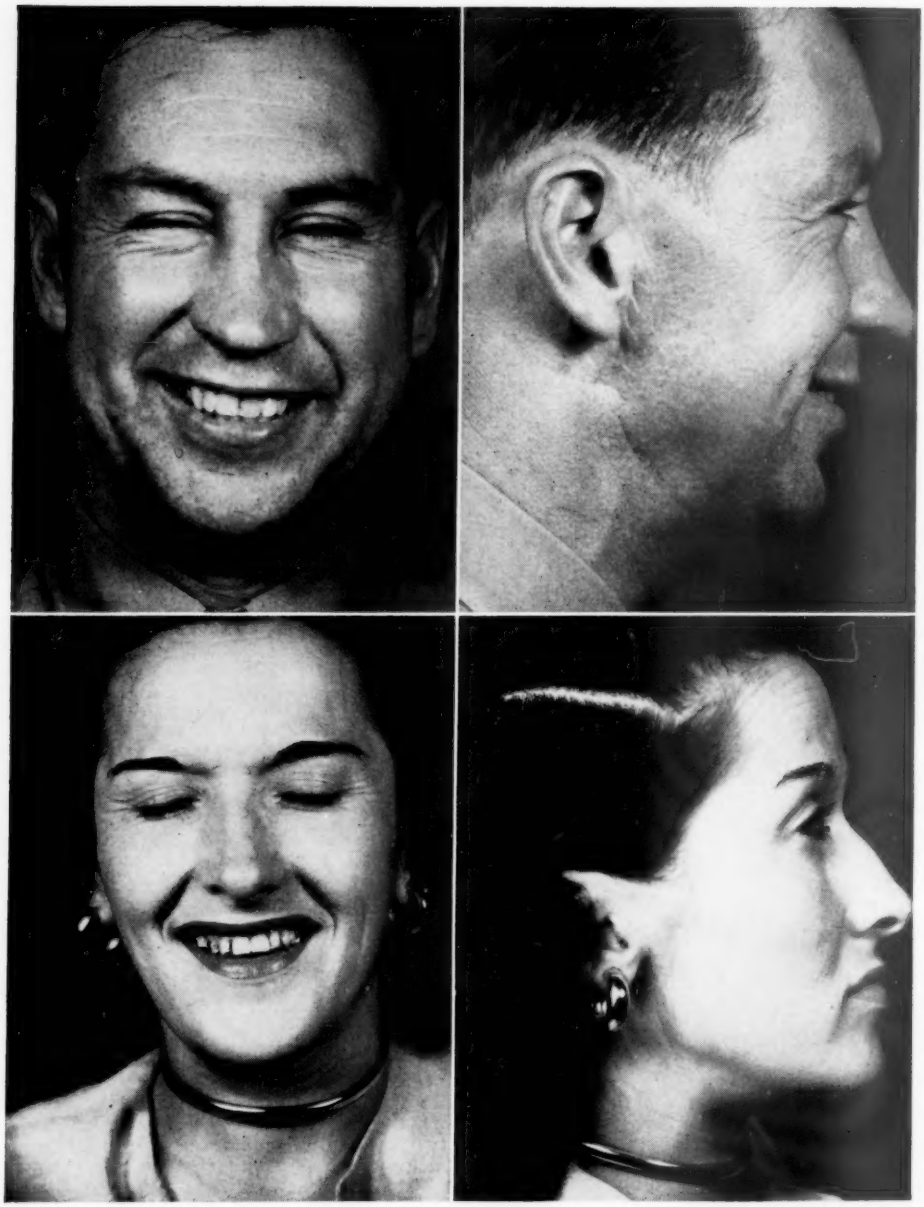


Fig. 6.

Fig. 5.—Photograph of the end results following radical parotidectomy.

Fig. 6.—Photograph reveals the functional end results of a radical parotidectomy. Note the perfect function of the seventh nerve. The loss of glandular tissue ordinarily produces very little deformity in facial contour.

X-ray therapy is currently combined with radical surgery only in those patients in whom there is deep invasion and it is judged at the time of surgery that eradication of tumor may have been incomplete. Radiation therapy as a

primary treatment is reserved for inoperable tumors and postoperative recurrences which have become inoperable. In the reported cases, 4 received x-ray therapy prior to the time they were seen for surgery, and in 3 the therapy antedated radical surgery by as long as 4 to 12 years. Two patients only received postoperative irradiation, given at the Tumor Institute of the Swedish Hospital (5,450 r. with 800 kv. in 26 days).

We cannot overemphasize to the surgeon who has not practiced radical parotidectomy for parotid tumors the virtue in this method of management. The surgeon can remain assured that his additional efforts to obtain exposure of the seventh nerve will be richly rewarded by the easy accomplishment of a difficult operation while employing the principles of sound tumor surgery. Individual experience of an extensive nature in the operative management of parotid tumors is not common among surgeons. The fact that outstanding medical centers report a 25 to 50 per cent recurrence rate in mixed tumors and a higher rate in carcinomas which cannot be identified specifically at the time of operation make us realize we are dealing with a formidable adversary. The survival and recurrence figures we have presented, although not followed unusually long for parotid tumors, indicate that early thorough treatment will produce successful results in a series of parotid tumors.

CONCLUSIONS

1. The treatment for parotid tumors is the performance of a radical parotidectomy early in the course of the disease.

2. The hazards and limitations of procedures such as enucleation, irradiation, and so forth must be realized if the recurrence rates are to be minimal.

3. Preservation of the seventh nerve is possible in all cases in which the nerve itself is not invaded by tumor. Adequate exposure, sufficient assistance, and careful dissection are paramount.

4. A surgical procedure has been outlined and the end results of 28 cases after a 10- to 15-year follow-up have been presented.

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CONTROL OF SURGICAL INFECTIONS AT THE MINNEAPOLIS GENERAL HOSPITAL

A Two-Year Study

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HEMOLYTIC *Staphylococcus aureus* infections are still threatening the lives of an increasing number of patients. It is evident that over the years this organism has adapted to antibiotics and continues to plague the medical and surgical profession throughout the world.[16] The recent false sense of security engendered by the appearance of potent broad-spectrum antibiotics has collapsed following critical evaluation of the problems of surgical infections as reported from hospitals in many countries.[1-2, 4, 5-6, 8, 9, 17] With regard to those strains of staphylococci which become indigenous to a given hospital, physicians must harken back to many of the principles of infection control that were effective in the preantibiotic era. Unfortunately, the environment of many modern hospitals constitutes a real menace to patients hospitalized therein since they are exposed to highly resistant strains of staphylococci through contacts with contaminated fomites, dust-laden air, and hospital personnel. During the early summer of 1956 the surgical staff at the Minneapolis General Hospital became alarmed over the mounting number of "clean" surgical wounds infected with staphylococci and a thorough study was organized. This paper deals with a series of investigations encompassing 25 months' operation of the Minneapolis General Hospital with regard to wound infections and the extent of the infection reservoir in our hospital.

THE STUDY PROGRAM

During July, 1956, an infection committee was formed to include the following members: the superintendent, the chief of surgery, a medical representative from the department of medicine, the chief operating room nurse and her assistant, the research bacteriology technician, the pathologist, the director of housekeeping, and the chief engineer. We were fortunate in having access to records of infections on the surgical services for an 8-month period prior to the formation of this committee since incident reports had been made out on all cases of infection, enabling us to make our study retroactive to Nov. 1, 1955.

The investigation was further benefited by an already established research program in the department of medicine studying all staphylococci and other

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pathogenic bacteria with antibiotic sensitivity studies of the organisms involved. The medical research laboratory was able to provide us with sensitivity patterns on all serious cases of infection on the surgical services from Nov. 1, 1955, onward. Specific proposals were made and changes in procedure were instituted on Aug. 1, 1956, and these will be discussed under the following headings.

Hospital-Wide Problem.—We were immediately aware that our problem was hospital-wide in scope since postoperative wound infections appeared on every operative service, and no individual or subservice team of surgeons was involved to the exclusion of others. Many portions of the Minneapolis General Hospital have been in use for over 50 years, and it was obvious that antiquated architectural design and functionally poor space arrangement posed difficult problems in light of modern concepts of infection control. The committee initiated studies in the operating rooms, on the surgical wards, in the laundry, in the emergency room, and in the central sterile supply room.

Character of the Hospital Population.—The Minneapolis General Hospital serves the community as an emergency center, an outpatient facility, and as an inpatient facility with all medical, pediatric, and surgical departments represented. During the course of a year the Minneapolis General Hospital treats approximately 45,000 people for a total of about 110,000 hospital visits or admissions. The preponderance of old and debilitated people on our inpatient services greatly heightens the risk of serious infections. In the emergency room, during 1955, there were 648 patients seen with an infection requiring either outpatient treatment or admission to the hospital. We are impressed with the large reservoir of infected patients that have to be managed in the inpatient and outpatient departments.

The surgical services are divided into a fracture and orthopedic service in one area of the building, and a soft tissue service in another area encompassing general surgery, neurosurgery, plastic surgery, urologic surgery, gynecologic surgery, chest surgery, and vascular surgery. In this presentation we shall speak of infections on the fracture and orthopedic service and the soft tissue surgical services (the latter to include all divisions detailed).

Operating Room Study.—During October, 1955, we moved into a remodeled operating suite newly equipped with an air-conditioning and cooling system. Immediately upon surveying our infection problem during July, 1956, the operating room circulating system was indicted as a possible potential source of air contamination during the course of surgery. Repeated studies using blood agar pour plates left open at various parts of the operating room during surgery and following routine daily cleaning indicated that organisms were brought to the operating room by patients and professional personnel but not through the air-conditioning system. Open blood agar pour plates were placed (1) in the stream of fresh incoming air, (2) to the room side of the first mechanical filter, (3) to the room side of the electrical filter, and (4) immediately under the dispersing filters in the ceiling (Fig. 1). At no time were *Staphylococcus aureus* colonies found in any pour plates during these repeated experiments.

TABLE I. OPERATING ROOM SURVEY RESULTS OF BLOOD AGAR PLATES EXPOSED TO AIR FOR 1 HOUR FOR CULTURE OF STAPHYLOCOCCUS AUREUS COLONIES (1956)

OPERATING ROOM	FEB. 29 (COLONIES)	APRIL 10	APRIL 23	JULY 9	JULY 24	SEPT. 11	SEPT. 25	OCT. 3
A	2	[4]	[4]	5	[110]	11	6	33
B	1	[12]	1	5	17	13	3	7
C	—	18	4	8	[240]	32	[14]	[5] [2]
D	22	5	1	[30]	20	[12]	—	17
E	[9]	6	17	7	11	15	[15]	7
	No explanation	Patient in E had staphylococcus in stools	No explanation	Open ulcer	C-Staphylococcal pneumonia	No explanation	Staphylococcal infection in C	+ Plates after cleaning room following staphylococcus case

□ Indicates *Staphylococcus aureus* colonies.

However, pour plates left open at various locations in the operating area did indicate that when patients known to have *Staphylococcus aureus* infections were moved about the operating suite colonies were found on pour plates many feet distant from the patient. In Table I we see the results of blood agar plate studies in the operating rooms on various days during 1956. Data are presented only for those days when *Staphylococcus aureus* colonies were present. On July 24, 1956, Room C was used for the bronchoscopic examination of a patient with staphylococcal pneumonia, and the extreme contamination of the environment is obvious. A relatively high count of staphylococcus colonies was obtained from Room A on the same day when a plaster cast was removed from a fracture patient prior to open surgery. It is inevitable that routine traffic of personnel spreads such contaminated air into corridors and other rooms in spite of positive pressure differentials maintained between each operating room and the corridor. We believe that in spite of the most vigorous precautions we endanger all other patients in an operating area when grossly infected patients are brought to the area of the operating rooms.

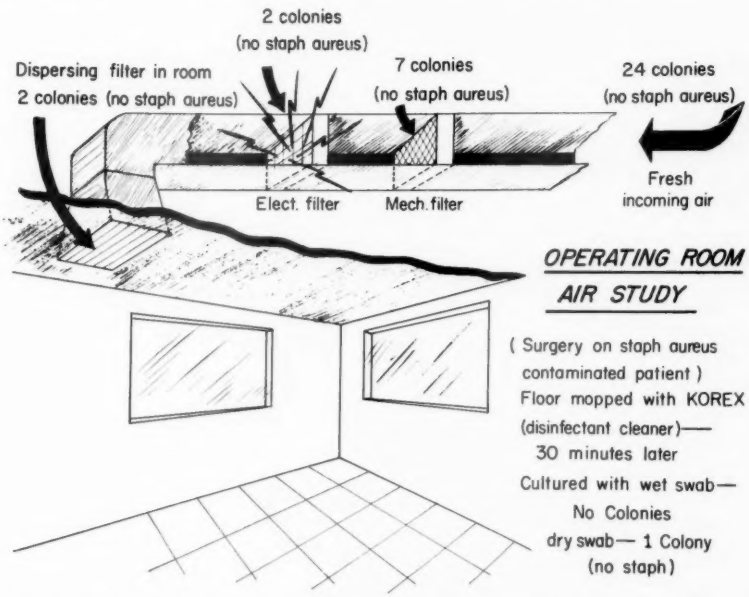

Fig. 1.—Repeated studies in operating rooms indicated adequate purification of air as it entered rooms. *Staphylococcus aureus* bacteria were always cultured from the air in the room whenever the patient harbored staphylococci on his body.

Repeated studies were performed testing the distilled water, normal saline, knife blades, suture tubes, sterile packs, instruments, lifting forceps, suture needles, and so forth, and we at no time obtained evidence that our autoclaves were functioning improperly or that contamination was carried to the operating table in the instruments or linen. The nursing staff was examined with throat cultures on 3 occasions and 4 of 12 people were found to have coagulase-positive staphylococci in their pharynx and hypopharynx. Sensitivity studies, however, indicated the strains of these organisms to be different from that resistant strain found commonly in the wounds on the wards of our hospital. We did not suspend any of our personnel from duty in the operating room on these

grounds and during the past 2 years only one student nurse was barred from operating room duty when she reported for work with furunculosis of the skin. (Studies of the floors of the operating room indicated contamination with *Staphylococcus aureus* colonies on blood agar plates following routine operations, but only an occasional colony appeared on wet-swab cultures after the floors had been mopped with an acceptable commercial disinfectant.)

Bacteriologic culture studies of the hands of the operating room teams prior to putting on sterile gloves indicated that our scrubbing techniques were apparently satisfactory. For several years we have used a basic 10-minute scrub of the hands and arms up to and including the elbows with one of 3 preparations; the personnel have the option of scrubbing with (1) a detergent containing hexachlorophene, (2) a liquid soap with hexachlorophene, or (3) gamophen bar soap. Hands and arms are rinsed in running water and dried on individual sterile towels; powder is applied in the scrubbing room, not in the operating room.

Following these studies it appeared to us that we probably were not contaminating the patient in the operating room either from the air-circulating system, the materials used in the operation, or the personnel involved in the surgery. (Everyone in our operating rooms including anesthetists and circulating nurses wear 2 standard masks covering both the nose and mouth.) Further, everyone who enters the operating rooms in our hospital *must* be properly gowned in scrub suits or dresses; infractions of this rule are considered by the infection committee and appropriate action is taken. We have been able to secure excellent cooperation in this regard from our surgical staff and associated personnel. Therefore, logically it seemed that the patients must be bringing staphylococcus organisms to the operating room on their skin and that perhaps these were not adequately removed with the skin preparation in use at that time.

Skin Preparation.—Prior to Aug. 1, 1956, the skin preparation at the Minneapolis General Hospital was as follows. (1) The night before surgery the area of the operation was shaved and scrubbed for 10 minutes with pHisohex or Germa-Medica; this area was not covered with a towel. (2) The following day in the operating room the area of operation was again scrubbed with pHisohex or Germa-Medica and then immediately treated with 4 applications of tinted aqueous Zephiran.

On review of this procedure we became concerned about the possible ineffectiveness of this technique and, on Aug. 1, 1956, instituted the following changes: (1) the night prior to surgery the area of operation was shaved and washed for 10 minutes with pHisohex or Germa-Medica; (2) the following day in the operating room (while the patient was still on the litter) the operative area was washed thoroughly four times with ether; (3) the patient was then moved into the operating room and placed on the operating table where the area of the operation was washed five times with 70 per cent alcohol (during this preparation the hands of the surgeon were scrubbed and gloved); and (4) the operative area was then painted with 5 applications of tincture of Zephiran. Drapes were applied in the usual manner.

Ether as an initial skin preparation, and a tincture as a final skin preparation, had been abandoned at the Minneapolis General Hospital several years ago with the advent of hexachlorophene-containing detergents and soaps. The use of open ether constitutes a fire and explosion hazard and early published results with hexachlorophene materials made their adoption into practice seem reasonable. However, under the emergency conditions of a high incidence of wound infections we felt that we should revert to a method of skin preparation which had been used for many years in many parts of the world and which apparently had given good results.

A subsequent study published in December, 1956, by G. F. Reddish indicated the reasonableness of these conclusions.[7] In Table II we see the results of skin bacteria reduction (using the serial-basin reduction method of testing) for all of the standard types of skin antiseptics now in use. From this table it is apparent that aqueous Zephiran as a skin preparation used immediately after washing the skin with a soap or detergent gave virtually no reduction in skin bacteria. On the other hand, alcohol as a 70 per cent solution gave excellent results by itself. Other types of antiseptics when applied to an alcohol-cleaned skin also had a relatively high degree of effectiveness. We feel that the data to be presented from our studies indicate the ineffectiveness of our former method of skin preparation.

TABLE II. SKIN BACTERIA REDUCTION, SERIAL-BASIN REDUCTION METHOD OF TESTING

ANTISEPTIC	CONTACT TIME	PER CENT REDUCTION SKIN BACTERIA
Iodine		
7 per cent tincture	30 seconds	100.0
5 per cent aqueous	2 minutes	99.5
2 per cent tincture	2 minutes	97.5
1 per cent tincture	2 minutes	94.5
Alcohol 70 per cent	2 minutes	88.0
Zephiran		
1:1,000 tincture (soap removed with rinse)	2 minutes	85.0
1:1,000 tincture (soapsuds rinsed)	2 minutes	80.0
1:1,000 aqueous (soap removed with rinse)	2 minutes	40.0
1:1,000 aqueous (soapsuds rinsed)	2 minutes	0.0
Alcohol 50 per cent—acetone 10 per cent	2 minutes	70.0
Alcohol 40 per cent	2 minutes	45.0
Metaphen 1:2,000 tincture	2 minutes	68.0
Mercresin 1:1,000 tincture	2 minutes	60.0
Mercurochrome 1:50 (alcohol-acetone-aqueous)	2 minutes	45.0
Mercuric chloride 1:1,000 tincture	2 minutes	30.0
Merthiolate 1:1,000 tincture	2 minutes	25.0

From G. F. Reddish.[7]

Statistical Results.—In our study of postoperative wound infections we decided to separate the surgical cases into those of so-called "clean surgery" as against those with "potentially infected or infected wounds." In computing our original data, operations performed on the nose and throat service and the proctology service were eliminated. During the 9 months from Nov. 1, 1955, to July 31, 1956, 1,374 operations were performed on the "clean" services and 41 postoperative wound infections occurred in so-called "clean cases." This represented a 2.98 per cent infection rate or one infection for every 33.5

operations performed. From Aug. 1, 1956, to Dec. 31, 1956 (5 months), a total of 806 operations were performed on these services and only 4 postoperative wound infections of the so-called "clean cases" resulted. This represented an infection rate of 0.48 per cent or one infection per 201.5 operations performed. This is an over-all improvement of 620 per cent for this period of time.

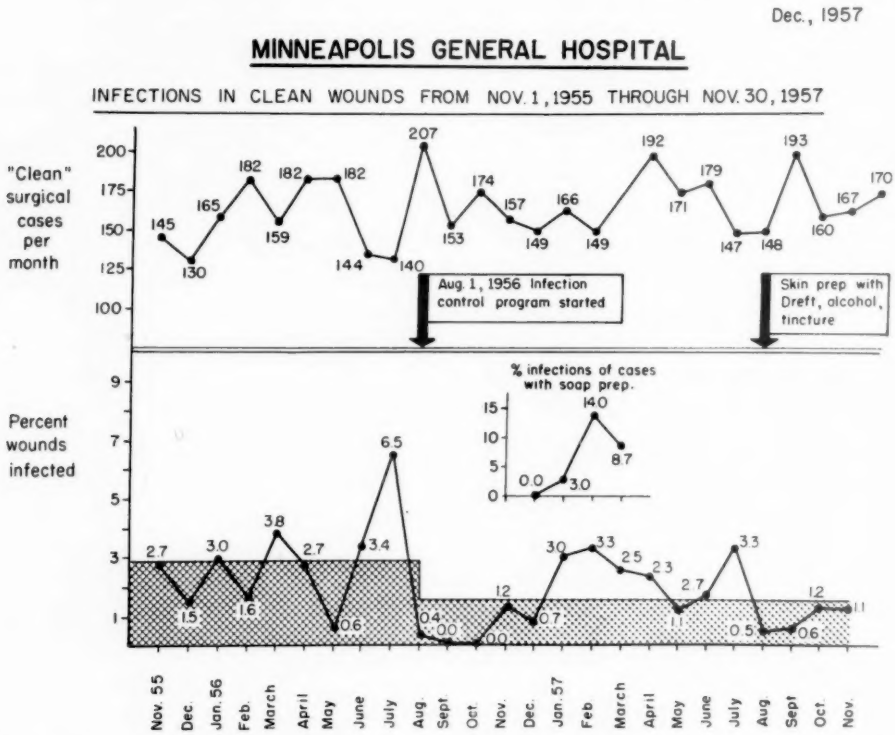
Dec., 1957
MINNEAPOLIS GENERAL HOSPITAL
INFECTIONS IN CLEAN WOUNDS FROM NOV. 1, 1955 THROUGH NOV. 30, 1957
"Clean" surgical cases per month
Aug. 1, 1956 Infection control program started
Skin prep with Dreft, alcohol, tincture
% infections of cases with soap prep.
Percent wounds infected
Nov. 55 Dec. Jan. 56 Feb. March April May June July Aug Sept Oct. Nov. Dec. Jan. 57 Feb March April May June July Aug Sept Oct. Nov.

Fig. 2.—Graph of clean wound infections during study period. The rise during December, 1956, and January, February, and March, 1957, probably was due to the high incidence of infections in one study room (14 per cent) where soap was again tried in place of ether for initial skin preparation under controlled conditions.

Fig. 2 presents the continuation of the infection study at the Minneapolis General Hospital up to Dec. 1, 1957. In this graph the percentage of "clean" wound infections is computed on the basis of the number of so-called "clean surgical procedures" performed during each month. The following types of procedures were removed from the total operating room report to arrive at the number of "clean cases": bronchoscopy, hemorrhoidectomy, fissurectomy, tonsillectomy, cystoscopy, incision and drainage of abscesses, skin graftings, application of simple plaster casts, and angiograms. As noted in Fig. 2, the peak of the infection problem in our hospital occurred during June and July of 1956. At that time we had an inordinate number of infections in our "clean" surgical cases and it was this experience that initiated the studies started on Aug. 1, 1956.

Our rate of infections in the "clean cases" dropped immediately, as has already been demonstrated, and the improvement has been sustained. The slight increase in wound infections during December, January, February, and

March of 1957 was due, we believe, to a change in skin preparations. At the request of the operating room nursing staff and the anesthesiology staff, who were hesitant to continue the use of ether as an initial preparation of the skin, we instituted a study in one operating room (Operating Room B) wherein all patients operated upon in that room had their skin prepared using liquid soap containing hexachlorophene in place of ether as the initial step in the skin preparation. A study of these cases later showed that, during the month of February, 14 per cent of the patients with skin preparations consisting of soap scrubs followed by applications of alcohol and tincture of Zephiran had a "clean" wound infection. This procedure was stopped during April, 1957.

At the suggestion of Dr. Carl Walter, who reviewed our infection problem at the Minneapolis General Hospital during May, 1957, we instituted the use of a simple detergent as the initial step in our operating room preparation of the skin on July 1, 1957. From that date to the present we have been using Dreft for an initial 10-minute scrub of the skin (the Dreft solution is rinsed away with sterile water) and then 5 applications of 70 per cent alcohol are followed with 5 applications of tincture of Zephiran. From Fig. 2 we see that the infection rate has continued at an acceptable low figure following the institution of this change in procedure. The over-all infection rate for the period of November, 1955, to July 31, 1956, was 3 per cent as contrasted with 1.48 per cent for the period of Aug. 1, 1956, to the present.

As mentioned earlier, all operating services in the hospital were involved with wound infections. However, the general surgical service, because of the increased number of patients operated upon, had the largest total number of infected cases. During the time of this study the fracture and orthopedic service had 23 clean wound infections or 2.3 per cent of the number of operations performed on their service, and the general surgical service including urology and gynecology had 57 clean wound infections or 1.3 per cent of the number of patients operated upon. Table III shows that 179 infection reports have been reviewed by the committee since the start of the study Nov. 1, 1955, and that 80 (44 per cent) have been classified as clean wound infections. An additional 57 patients had infections of wounds where contamination was indigenous to the pathologic problem under treatment and where subsequent infection was not considered as attributable to poor technique in any aspect of the care of the patient. Included in this group are problems such as gunshot wounds, compound fractures, perforated viscera, ruptured bowel, peritoneal abscesses, and so forth.

TABLE III. CLEAN WOUND INFECTION ON SERVICES
(November, 1955, to December, 1957)

Fractures and orthopedics	23	1,000 cases—2.3%
Soft tissue service	57	4,489 cases—1.3% (Gynecology—4) (Urology—3)
Total	80	
Total infections reported on surgical services in 25 months—179*		

*Clean wound infections were 44% of total.

Bacteriologic Studies.—The tube dilution method of testing for antibiotic sensitivity has been used at the Minneapolis General Hospital for several years. Fig. 3 gives the sensitivity patterns of 35 staphylococci cultured from surgical wound infections, indicating that 22 of these organisms had an almost identical antibiotic sensitivity pattern. This pattern of sensitivities has recurred in our hospital with monotonous regularity and we consider this organism to be the strain indigenous to our hospital. The other 8 organisms in column 2, and 5 organisms in column 3 probably represent bacteria brought into the hospital by patients and the sensitivity patterns are only grossly grouped. We did not perform bacteriophage typings of these bacteria but it is the consensus of our bacteriologic consultants that the high degree of consistency in the sensitivity patterns of our indigenous strain indicates uniformity of the strain of the organism.

MINNEAPOLIS GENERAL HOSPITAL

HEMOLYTIC STAPHYLOCOCCUS AUREUS, COAGULASE POSITIVE
"MICROCOCCUS PYOGENES VAR. AUREUS"

SENSITIVITY	*22*		*8*	*5*
Achromycin	100-200	Micrograms per c.c. to inhibit growth / Minimal inhibiting concentration	100-200	6.3-25
Streptomycin	>800		100-800	6.3-25
Chloromycetin	6.3		6.3-50	6.3-12.5
Penicillin (units)	>800		50-800	.09-800
Bacitracin (units)	1.5		1.5-3.1	3.1
Ilotycin	800		.19	.19-.38
Neomycin	1.5-3.1		1.5-3.1	1.5-6.3
Albamycin	1.5-12.5		1.5-3.1	.75-6.3
Sigmamycin	6.3			
Matromycin	3.1			
Magnamycin	1.5			

Fig. 3.—Twenty-two of 35 staphylococcal organisms studied during one period had identical sensitivity patterns. This constitutes our highly resistant "hospital" strain. The other organisms can only be roughly grouped and were undoubtedly brought into the hospital by the patient involved.

Our ability to control the *Staphylococcus aureus* organism in the patients undergoing surgery is demonstrated in Tables IV and V. From Nov. 1, 1955, to July 31, 1956, 41 patients had clean wound infections and 32 contained the hemolytic *Staphylococcus aureus* organisms. During this same period of time there were 11 of 16 patients treated on the surgical wards for pre-existent *Staphylococcus aureus* infections. From Aug. 1, 1956, to Dec. 31, 1956, only 4 patients had infections in clean surgical wounds and of this number only one had a hemolytic *Staphylococcus aureus* infection. Correspondingly, of 14 patients on the surgical services during the same period of time with preinfected wounds, there again were 12 that had hemolytic *Staphylococcus aureus* cultured from the wound. It seemed to us that the preparation of the skin of our patients prior to surgery was a key factor in the control of the problem of surgical infections with hemolytic *Staphylococcus aureus* in our hospital.

TABLE IV. BACTERIA CULTURED FROM INFECTED WOUNDS
(Nov. 1, 1955, to July 31, 1956)

ORGANISMS	NUMBER OF PATIENTS WITH CLEAN WOUNDS INFECTED	NUMBER OF PATIENTS WITH PREINFECTED WOUNDS
Hemolytic *Staphylococcus aureus*, coagulase positive	24	9
Staphylococcus aureus and beta hemolytic streptococcus	7	2
Staphylococcus aureus and pseudomonas	1	-
Total *Staphylococcus aureus*	32 (78%)	11 (68%)
Hemolytic *Staphylococcus albus*	6	3
Hemolytic *Staphylococcus albus* and beta hemolytic streptococcus	2	-
Escherichia coli and hemolytic streptococcus	1	-
Proteus—*Escherichia coli*—pseudomonas	-	1
Proteus—hemolytic streptococcus—pseudomonas	-	1
	41	16

TABLE V. BACTERIA CULTURED FROM INFECTED WOUNDS
(Aug. 1, 1956, to Dec. 31, 1956)

ORGANISMS	NUMBER OF PATIENTS WITH CLEAN WOUNDS INFECTED	NUMBER OF PATIENTS WITH PREINFECTED WOUNDS
Hemolytic *Staphylococcus aureus*, coagulase positive	-	9
Hemolytic *Staphylococcus aureus* and beta hemolytic streptococcus	1	1
Hemolytic *Staphylococcus aureus* and gamma streptococcus	-	2
Total *Staphylococcus aureus*	1 (25%)	12 (85%)
Hemolytic *Staphylococcus albus*	2	1
Hemolytic *Staphylococcus albus* and beta hemolytic streptococcus	-	1
Beta hemolytic streptococcus	1	-
	4	14
Comparison of Tables IV and V		
Staphylococcus aureus infections prior to hospital changes—9-month period	41 (78%)	16 (68%)
Staphylococcus aureus infections after initiating hospital changes—5-month period	4 (25%)	14 (85%)

Ward Problems.—Surgical inpatients at the Minneapolis General Hospital are cared for in 6 large wards with 20 (or more) beds per ward. We have only 2 private rooms for the isolation of infected cases, and cross-contamination and cross-infection problems are always pressing. During 1956 air contamination culture studies were made on the fracture wards and colonies of *Staphylococcus aureus* were obtained on blood agar plates in all areas of the wards at varying times of the day. Changing bed linen did not seem to increase the colonies of staphylococci, but bedding and furniture surrounding patients harboring staphylococcic infections were found to be heavily contaminated. Thorough cleansing of the surgical wards following removal of patients and use of disinfectants on the floor made the areas safe as far as test results with blood agar plates were concerned. Cross contamination from patient to patient has apparently been an important problem in our hospital as exemplified

by the fact that, prior to Aug. 1, 1956, blankets for use during the night were indiscriminately passed out in the evening and collected and indiscriminately stored during the day. After Aug. 1, 1956, all material incident to a given patient's case, including blankets and bedding, has been retained for that patient only.

Studies of the laundry function demonstrated very little in the line of procedures to be implicated in the over-all infection problem. Our laundry has been operating under recognized regulations approved by the national hospital boards. The extension of these studies into areas such as the physiotherapy section indicated that hemolytic staphylococci could be cultured on dry swabs from whirlpool tanks that had been cleaned following the treatment of infected patients. Studies of fomites such as instruments used to remove plaster casts on the wards indicated gross contamination of the cast-cutting equipment. Routine sterilization between use was instituted as of Aug. 1, 1956. Water carafes at the patient's bedside are sterilized each day in our hospital and do not constitute a bacterial multiplier problem in our hospital.

The technique for the care of wounds on the wards was improved and personnel were instructed to use gloves in the examination of patients with colostomies or ileostomies, and whenever changing dressings on the patients with infected wounds.

Changes instituted in the management of the wards were as follows: (1) improved technique for wound care during rounds; (2) the use of gloves to examine colostomy and ileostomy patients; (3) wound dressings were discarded after the first 24 hours; (4) patients with infections were segregated in one area of the wards, and where possible they were hospitalized on the contagion service; (5) the use of brooms for sweeping was discontinued and floors were to be cleaned only with oil or water mops, with the wet mopheads stored overnight in disinfectant; (6) the interchange of extra blankets and any other items incident to the care of a patient was stopped; (7) cast cutter heads and other equipment of this type were sterilized after each using; and (8) strict gowning and masking techniques around infected and isolated patients were rigorously enforced.

Dollar Cost of Clean Wound Infections.—It is impossible to estimate the over-all effect of serious wound infections upon the subsequent lives of patients, but it is obvious that older, more debilitated patients frequently die of infections with hemolytic staphylococci. The mortality due to staphylococcal infection among the patients discussed in our report during its early phases from November, 1955, to March, 1956, was 13 per cent. Many of these patients, who died of their infections, were in the older age group and had suffered serious fractures or had undergone a major abdominal operation. In each instance, however, the infection was considered a prime factor in the patient's demise.

In addition to the morbidity suffered by the patients, the economic factors of clean wound infections loom large. Table VI represents an attempt to estimate the dollar cost of postoperative wound infections in the "clean cases" at the Minneapolis General Hospital during 1956. The actual days in the hospital

are listed in the fourth column and the estimated excess hospital days are listed in the fifth column. For the 45 patients involved with clean postoperative wound infections during 1956 the total of excess number of days of hospitalization is 2,480. With an over-all hospital cost per patient per day at that time of about $32.00, the annual cost on this basis would be approximately $79,000.00. It is significant that during the current year of 1957 we have had only an occasional patient who has had to be hospitalized for an excessive length of time due to serious wound infection. The infections that are reported in the data for 1957 in the main are of lesser severity and have cleared up more readily than those reported in the earlier parts of the study.

TABLE VI. ESTIMATE OF DOLLAR COST OF CLEAN WOUND INFECTIONS DURING 1956
(Minneapolis General Hospital)

PATIENT	AGE	OPERATION	DAYS IN HOSPITAL	EXCESS HOSPITAL DAYS	COMPLICATION
G. S.	68	Cholecystectomy	42	30	Wound infection
L. P.	40	Transaxillary sympathectomy	80	70	Empyema
H. O.	60	Herniorrhaphy	60	55	Wound infection—scrotal infection
L. L.	64	Hysterectomy	90	80	Abdominal wound infection
D. Y.	51	Gastrectomy (duodenal ulcer)	75	65	Wound infection
C. S.	26	Nephrectomy	35	25	Deep flank wound infection
L. W.	54	Colon resection	35	25	Wound infection
R. G.	64	Cholecystectomy	42	32	Wound infection
N. J.	56	Hiatus hernia repair	42	32	Wound infection
J. L.	49	Gastrectomy	42	32	Wound infection
				446 days	

Total days excess hospitalization for 45 patients—2,480.
Hospital cost for 1 day—$32.00; annual cost—$79,360.00.

DISCUSSION

The management and control of infections in any hospital constitutes a problem unique to that given hospital. While certain basic principles can be applied in many cases, variations in building design, types of function of individual units, the type of hospital personnel involved, type of patient load, and so forth, necessitate an individualized approach to the problem. We believe one of the most important and basic steps for any hospital program is the establishment of an infection committee.

In surveying the Minneapolis General Hospital for its problem regarding postoperative wound infections we have been impressed with the number of conditions that work to our disadvantage and which must be accepted and circumvented in some way. Ideally we could probably improve our control of the infection problem in our hospital by very extensive remodeling of all patient areas. However, at present this is unrealistic and impossible to achieve. We must, in order to perform our function, accept the inadequacies and disadvantages inherent in our old and poorly designed structure and search for methods of controlling our surgical wound infection problems in less extensive and expensive ways.

Since our hospital is a teaching unit, affiliated with the University of Minnesota Medical School, we must also accept the presence of large numbers of interested bystanders at all phases of the care of our patients. There is no possibility of truly limiting the amount of traffic in our operating rooms since our students must have the opportunity to witness surgical procedures, and we have no observation domes or balconies. In addition, the surgery performed at the Minneapolis General Hospital is primarily done by the resident staff, under the supervision of the full-time and attending surgical staff. Inevitably, many of our operations are prolonged because of inexperience on the part of the operators and surgical technique is obviously being learned. However, we feel that the accomplishment of such a low rate of surgical infections among our clean surgical patients is a tribute to the soundness of the changes instituted by the infection committee in the face of our many and varied problems.

The character of the patient load in our hospital also predisposes our surgical services to an increased problem of controlling wounds. Healing is slow and of poor quality in many of our older and debilitated patients, and a fair portion of our younger patients is either chronic alcoholics or has already the deleterious effects of cirrhosis of the liver. Our vascular surgical service has a high percentage of diabetic patients and older arteriosclerotic patients with peripheral ulcers and gangrene, all infected with staphylococci. The infection reservoir problem in our hospital is perhaps the most acute of any hospital in the Minneapolis area. It is common to see one or two serious carbuncles on the surgical services each month. The number of patients with infections entering the emergency portion of the hospital each year is great (550 to 650). The problems of patient care are amplified many times over because of the open ward conditions under which we must operate. Our unit for contagious disease is frequently overcrowded with serious cases of meningitis, poliomyelitis, and so forth, and the opportunities for isolating our patients with staphylococcic infections are poor. It is against this background that we have attempted to improve the situation of postoperative wound infections in our hospital.

The only acceptable incidence figure for postoperative wound infections would be the complete absence of infection in all postoperative clean surgical cases. We believe the attainment of an over-all infection rate in the clean surgical cases of 1.5 per cent is a significant achievement. Since it is impossible for us to adequately control so many of the factors involved in this problem in our hospital, the changes in skin preparation prior to surgery appear to be a significant factor. In other words, we cannot expect to adequately prevent contamination of our patients with the hospital strain of *Staphylococcus aureus* prior to their operations, and, therefore, the problem in our hospital seems to revolve about the adequate removal of such organisms just prior to, and at, the time of surgery.

We are satisfied that all of the changes instituted throughout our hospital during the past 18 months have contributed in some measure toward better control of wound infections. It is noteworthy that the improvement in the infection problem has persisted in our hospital for over 12 months, even during the heat

of the summertime. With no facilities for air conditioning in any areas other than the operating suite, the wound infection problem conceivably becomes considerably more serious during the hot summer months. We believe that under conditions existing in our hospital we cannot control infections by the prevention of contamination of the preoperative patient's skin. We have accepted the challenge of accomplishing everything possible at this end of the infection spectrum, but we fully realize that in most cases we will have to catch the patient at the operating room door and remove the offending organisms before the knife is laid to the skin.

Continual surveillance of all aspects of our operating room technique is observed, and such vigilance is undoubtedly important to the continuation of successful surgery without complication of infection. Of the 80 patients with clean wound infections during this 25-month study, 11 (13.7 per cent) had a surgical technical error that might be responsible in large measure for the patient's infection. In a teaching hospital such as ours continual vigilance is the order of the day in orienting young surgeons in the proper technical approach to their various problems.

Improvements in many aspects of our hospital function are still being effected. It is our hope that, with continual vigilance and continual study, the outlook in the infection problem at the Minneapolis General Hospital will continue to improve.

SUMMARY

A 2-year study on the problem of "clean" wound infections has been presented from the Minneapolis General Hospital. During the study period, a significant improvement has been made in the number of "clean" surgical cases developing staphylococcic wound infections and the following remedial measures appear to be of significance: (1) monthly meetings of a recently established infection committee have continued to review the special reports made out on all patients with wound infections, and the tabulation of these problems on the surgical services has permitted statistical analysis of our results; (2) in the absence of adequate facilities for complete isolation of all patients infected with staphylococci, the prevention of cross contamination on the open wards has been aided by stopping the interchange of blankets and fomites between patients and by improving dressing techniques; (3) the preoperative skin preparation has been changed from soap or hexachlorophene solution and aqueous Zephiran to ether and alcohol and tincture of Zephiran. During the latter phases of this study Dreft has replaced the initial ether rinse and the results appear to be satisfactory; and (4) improvements in housekeeping procedures both in the operating rooms and on the surgical wards have undoubtedly been of value.

During the early phases of this study an improvement of 620 per cent was made in the rate of clean wounds infected with staphylococci, and the improvement has continued quite well to date. At present the over-all infection rate on the clean surgical services at the Minneapolis General Hospital is less than 2 per cent.

Bacteriologic sensitivity studies of the staphylococci involved in our infections yielded a common pattern of antibiotic resistance for a high percentage of the staphylococci involved. This common organism is undoubtedly a strain of staphylococcus indigenous to our hospital and which contaminates the skin, nasal passages, and gastrointestinal tract of our patients during the course of their hospitalization. We must accept responsibility for the obvious fact that all patients confined to our hospital for an extended period of time prior to surgery are exposed to these highly dangerous bacteria. In the future, the control of antibiotic resistant staphylococci looms as one of our most pressing problems with regard to adequate and safe performance of clean surgical procedures.

We are satisfied that this problem can be controlled in a large city hospital involved in a teaching program including medical students, interns, and residents if common sense techniques of asepsis and antisepsis are instituted in the proper manner. However, constant vigilance on the part of the entire hospital staff is mandatory if improvements are to continue indefinitely.

We wish to express our gratitude to the following personnel of the Minneapolis General Hospital for their splendid cooperation in conducting these studies: Mr. Donald Smith, Superintendent, Mrs. Moe and Mrs. Kalscheuer, Surgical Floor Supervisors, and Miss Georgia Nobles, Director of Nursing.

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OBSERVATIONS ON INTRAPERITONEAL ADHESIONS

An Experimental Study

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THE formation of adhesions represents a phase in the dynamic healing process to peritoneal injury. Trauma, whether mechanical, bacterial, or chemical, appears to be the etiologic agent in the production of adhesions. The extent of the intraperitoneal reaction tends to reflect the degree of damage inflicted. Some adhesions have been observed to form and then resorb, leaving a free peritoneal cavity.

Efforts have been made in the past to create adhesions with certain agents and then various devices were employed to prevent their recurrence.[3-5, 7, 9, 12, 15-17, 19, 20] In the first part of this study, no attempt was made to traumatize the bowel or peritoneum other than the injury produced by a laparotomy with insertion of a plastic window into the anterior abdominal wall of the animal. In the second phase of this study, additional factors were added during and after the stage of fibrinous resolution so that they might be evaluated in the production and maintenance of adhesions. It was well documented that chemical agents such as turpentine, iodine, and phenol could incite very extensive adhesions so that no effort was made to recapitulate those facts.[2]

The following observations represent a pathophysiologic study of the natural evolution of intestinal adhesions as visualized through a transparent plastic window in the abdominal wall of the dog.

METHOD

Eight dogs weighing at least 20 Kg. were used in the study. A 6 by 8 cm. elliptical Plexiglas window with a 90 to 92 per cent light transmission and a haze of 5 to 10 per cent was utilized. The windows were contour shaped for each dog. A screw tap was placed at one end of the window so that measurements could be taken or fluid aspirated without removing the window. A stainless steel foundation mesh was sutured around the window with wire. After the rectus muscles had been excised, the window was sutured between the anterior and posterior fascial sheaths. Sterilization of the window was accomplished with 1:1,000 Zephiran solution for 24 hours. Approximately 2 hours were consumed in performing the laparotomy and insertion of the plastic window in the fascial compartments.

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The omentum was excised so that the actual bowel mechanics could be observed. In 3 control animals in which the omentum was not excised, the sequence in adhesion development or resolution was not altered. The omentum participates as any capillary-containing organ in adhesion formation.

Female dogs were chosen whenever possible because there is greater space in the anterior wall and urine which was a constant contaminant in the male dog was avoided. Nembutal anesthesia (20 mg. per kilogram) was utilized during the experiment.

The plastic window provided easy visual access to the peritoneal cavity and photographs were taken without event. The sequence in the development of peritoneal adhesions was identical in the 8 animals. The variations were attributable to the degree of trauma and the age and general condition of the animal. The 8 animals were used repeatedly in the 2 phases of the experiment culminating in induced peritonitis. The dogs were observed for 1 to 6 months.

NATURAL HISTORY OF FIBRINOUS ADHESIONS POSTLAPAROTOMY

Observations represent an average in occurrence and time in the formation of intestinal adhesions in 8 animals.

TABLE I. RESPONSE OF PERITONEUM AND BOWEL TO LAPAROTOMY AS OBSERVED THROUGH A PLASTIC ABDOMINAL WINDOW

HOURS AFTER LAPAROTOMY	CAPILLARY DILATATION	CAPILLARY STASIS	PERITONEAL FLUID	FIBRIN	ARTERIAL PULSATIONS	PERISTALSIS	DILATION OF BOWEL
2	++	0	++	0	++	++	0
4	+++	+++	++++	++	+	+	0
6	++++	++++	++	+++	+	+	++
12	++++	++++	+++	++++	+	+	++
18	++++	++++	++	++++	+	0	+++
24	++++	++++	++	++++	0	0	++++
36	++++	+++	++	++++	0	0	++++
48	++++	++	+++	++++	0	+	++++
60	++++	++	++++	+++	+	++	+++
72	++	++	+++	+	++	++	++
84	+	0	++	0	+++	++	++
96	+	0	+	0	+++	+++	0

If gross disruption in the serosa or mesothelium occurred, a firmer, stronger, fibrinous adhesion was noted, and, if it remained longer than 5 days, permanent fibrous adhesions resulted. Once a fibrous adhesion was formed, it became thinner and shorter but it did not resolve (Fig. 1).

FACTORS WHICH ALTERED RESOLUTION OF FIBRINOUS ADHESIONS

Infection.—Peritonitis from mixed intestinal flora was induced by inoculation of the peritoneal cavity with the feces of the animal. This fecal contamination was thought to reflect the typical case of peritonitis. The peritoneal response was dependent upon the virulence and number of bacteria plotted against the tissue resistance. If the fluid was less than 100 c.c., the peritonitis frequently began as nodular areas of pus (Fig. 2). If the organisms were not

destroyed by animal defenses, there was a gradual coalescence of the excrescences of fibrinous exudate to cover the intraperitoneal contents in a thick, creamy blanket. The pus was often localized with this type of infection. Five animals that exhibited this type of peritonitis survived.

Fig. 1.—A fibrin film encompasses inactive, dilated bowel 24 hours after insertion of Plexiglas window.

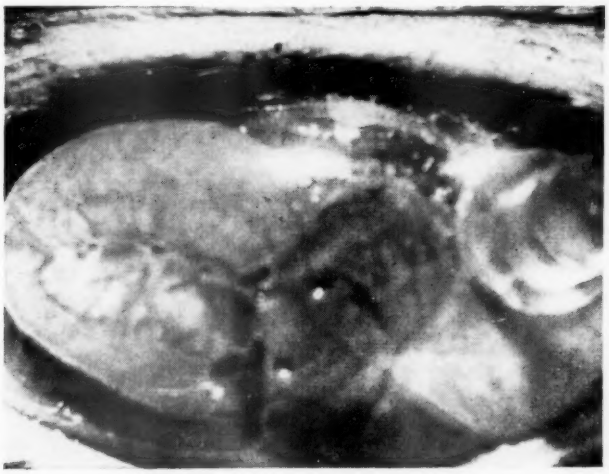

Fig. 2.—Induced peritonitis in the presence of less than 100 c.c. of peritoneal fluid began as nodular areas of pus. Note deposits along mesentery and bowel wall of the U-shaped loop of the small intestine in this dog.

If there was over 200 c.c. of intraperitoneal fluid at the onset of peritonitis, bacterial invasion was extensive with all areas involved in the reaction. Two of 3 animals died with this type of peritonitis. The greatest volume of intraperitoneal fluid occurred between the second and fourth days following laparotomy. The fluid increase corresponded with the peak of capillary exudation and fibrinous resolution.

Adhesions in the presence of infection were often lifesaving by their ability to localize the pus in the flanks or contiguous to the anterior abdominal wall. Rarely was the pus localized between the loops of bowel. In most instances one surface of the abscess consisted of peritoneum. In those animals with the

plastic window replacing the anterior abdominal wall, there was a tendency for the pus to localize between the adherent loops of bowel and the plastic window. It seemed that as the fibrinous exudate became organized, the collections of infected fluid were pushed away from the intestinal tract.

If infection was induced before the stage of fibrinous resolution was completed, the resorption was halted and additional fibrin was laid down. If infection occurred after the stage of resolution, the afore-mentioned inflammatory response was recapitulated. Many adhesions were resorbed in the presence of peritonitis, but their resolution was dependent upon the degree and duration of the bacterial trauma and the age and physical condition of the experimental animal.

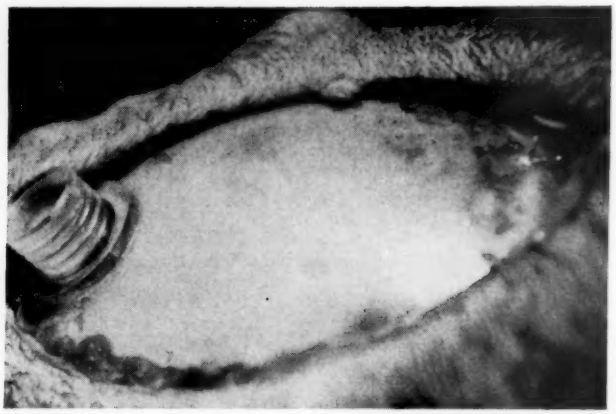

Fig. 3.—Induced peritonitis became diffuse if there was an abundance of fluid in the peritoneal cavity at the time of contamination.

Blood.—Since free blood was frequently found in the peritoneal cavity, it was of interest to determine the fate of clotted and free blood. Free blood (100 c.c.) was absorbed in the 8 animals in 48 hours. A 4 cm. well-formed clot was slowly destroyed and completely resorbed in 8 days. It was believed that blood and clot played no role in the production of adhesions other than providing an excellent medium for invading infection.

Heparin and Streptokinase-Streptodornase.—These agents were employed to note their effects on the natural history of the adhesion. Heparin prevented the formation of the fibrin deposits but had no effect once the fibrin film was present. Streptokinase which activates fibrinolysin was found to dissolve the fibrinous adhesions but had no effect upon organized adhesions. Both of these agents prevented adhesions in a different phase of their evolution. If either heparin or streptokinase was used, there was very little localization of the peritonitis with a more severe systemic response in the experimental animal. Hemorrhage was not observed as a complication of heparin administration. Those observations have been made previously in a larger controlled series and no effort will be made to belabor the points.[2]

Plexiglas Window.—After periods of 20 to 30 days, there was a tendency toward reperitonealization with wound contracture under the Plexiglas window.

The plastic window, no doubt, represented an intraperitoneal foreign body which may not have been inert chemically. If the adhesions were lysed through a separate laparotomy incision, the entire process was repeated with what appeared to be more adhesions each time lysis was performed. Apparently the increased trauma that was required each time the adhesions were divided produced a greater fibrinous response which exhibited less chance of resolution. Fibrinous bands which were divided bluntly produced a greater number of permanent adhesions.

Fig. 4.—This Plexiglas abdominal window has been in situ for 2½ weeks. After this period of time, there is a tendency toward reperitonealization and wound contracture.

DISCUSSION

The formation of peritoneal adhesions is a dynamic, nonspecific, indiscriminate response of the organs to injury. The natural history of the typical postoperative adhesions appears to be trauma, capillary dilatation, stasis in capillaries, increased capillary permeability, fluid loss intraperitoneally and into the bowel wall, fibrinous exudate, decrease in pulsations in vasa rectae, relative anoxemia, diminution in peristalsis, release of enzymes from white blood cells, increase in intraperitoneal fluid, resorption of fibrin, recanalization of capillaries, return of arterial pulsations, and resumption of peristalsis. Greater than usual trauma lays the scaffolding for lasting fibrous adhesions.

From the onset of the trauma to the return of normal function of the bowel requires from 72 to 96 hours depending upon the age and condition of the animal and the magnitude of the procedure. The capillary wall seems to be the controlling factor in the production of the adhesion. Krogh,[10] in his studies on the tongue of the dog, was able to show that the capillary activity was independent of the blood pressure. Nervous, chemical, mechanical, and thermal stimuli were responsible for the contractile features of the vessel. The stasis which occurred in the capillary was due to the dilatation from the various stimuli applied. Landis,[11] using the micropipette technique for cannulation of the capillary was able to corroborate the high degree of capillary permeability which readily furnished fibrin under traumatic conditions.

The homeostatic function of the white blood cells in the release of proteolytic enzymes appears to be responsible for the fate of fibrinous deposits. Opie[14] in microscopic observations on inflammatory exudate noticed an increase in polymorphonuclear leukocytes in the exudate within 6 to 24 hours after trauma. He further described a disintegration of the leukocytes in 72 to 96 hours with the release of proteolytic enzymes. Those enzymes, he thought, were responsible for the breakdown of the fibrinous network and its subsequent absorption into the lymphatics. If the inflammatory exudate persisted longer than 96 hours, the macrophages played a larger role in the resolution of the process. Barnes[1] was able to confirm the presence of numerous proteolytic enzymes in the inflammatory exudate of cats and rabbits.

Florey[6] in observations on the frog mesentery noticed reconstitution of the integrity of the capillary wall and opening of the venous end of the capillary with a return in normal blood flow through the capillary circuit in 48 to 96 hours. Jackson's[8] unpublished data employing a microglass electrode and an oxygen tensiometer found an increase in hydrogen ion concentration and a relative anoxemia in adynamic ileus which occurs postlaparotomy. The decrease in blood flow in the capillaries and arterioles in the face of intraluminal distention, interstitial edema, and fibrinous exudate seems adequate to account for the relative oxygen lack of the bowel wall.

During the period of maximal capillary exudation there is a concomitant ileus of the bowel. The lack of intestinal motility increases the agglutinating effects of the fibrinous exudate between the adjacent loops of bowel and incised peritoneum. However, attempts to increase intestinal activity, using Pituitrin or physostigmine to prevent adherence in a limited number of experiments on dogs, suggested that those agents potentiated adynamic ileus and fibrinous deposits by anoxia to the bowel wall. Additional experiments will be necessary to corroborate those impressions. Ochsner and associates[13] have shown that motility per se will not prevent the formation of adhesions if the damage inflicted is severe enough.

The impression was obtained that gentle intestinal motility augmented fibrinous resolution on the third and fourth days postlaparotomy by the simple mixing effects of the enzymes and fibrin. Normal intestinal activity was also observed to make permanent adhesions thinner and longer. The broader, firmer, more vascular adhesions were observed in the flanks, pelvis, and adjacent to the liver, stomach, and spleen.

Studies by Stearns,[18] using the Sandison-Clark chamber in the rabbit's ear, disclosed the ingrowth of capillaries into the fibrinous adhesions from the fourth to the seventh days. Fibroblasts were noted on the sixth day. As time elapsed, collagen fibers were laid down and by 2 or 3 weeks contracture of the wound was noted.

The time relations in the gross appearance of the natural history of the intestinal adhesion appears to coincide with the observations of the uncomplicated healing process in other parts of the body. All organs containing blood

vessels are capable of fibrin deposition and healing by fibrosis. Even though the healing process seems to be the same, there are some fundamental differences between adhesions in a serous cavity and healing in solid tissues. Serous cavities are physiologically constructed to permit motion of the indwelling organs. The intraperitoneal organs lie in a closed cavity (except in the female) of mesothelium. If the peritoneum is not damaged, adhesions form between the margins of other intraperitoneal organs. If both bowel and peritoneum are traumatized, there may be ready adherence of the 2 organs during the period of adynamic ileus. If the trauma has been adequate, the fibrinous adhesions will be replaced with fibrous bands. The bands contract along their long axes between the bowel and peritoneum and along the short axes of the wounds incurred on the bowel wall or the peritoneal surface. This process of shortening does very little damage to the peritoneum, but it may distort the bowel by an anterior or lateral pull on an isolated point on the bowel. A kink in the bowel may also result from the shortening of the base of the adhesion attached to the bowel wall. Adhesions between adjacent loops of bowel seldom produced difficulty in these animals. The results of unyielding contracting fibrous tissue are apt to be seen concomitant with intestinal hyperactivity or distention.

SUMMARY AND CONCLUSIONS

1. A method using a Plexiglas window for study of adhesion formation in the dog is described.

2. The natural history of the adhesion postlaparotomy appears to be trauma, capillary dilatation, stasis, increased capillary permeability, fluid loss, fibrinous exudate, decrease in pulsations in the vasa rectae, relative anoxemia, diminution in peristalsis, release of proteolytic enzymes from white blood cells, increase in intraperitoneal fluid, resorption of fibrin, recanalization of capillaries, return of arterial pulsations, and resumption of peristalsis.

3. The extent of adhesion development is directly proportional to the injury whether it be chemical, bacterial, thermal, or mechanical.

4. Peritonitis productive of heavy fibrinous exudate frequently results in broad, vascular, permanent, fibrous adhesions.

5. Blood, free or clotted, in the peritoneal cavity does not incite adhesion formation but provides an excellent medium for bacterial contamination which may subsequently be responsible for numerous dense adhesions.

6. Heparin inhibits adhesions only before the stage of fibrinous deposition, whereas streptokinase which activates fibrinolysin destroys the early fibrinous film. Those agents tend to inhibit localization of infection when they are used intraperitoneally.

7. Induced intestinal hypermotility to prevent adhesions seems to perpetuate a normal tissue response to injury. The hyperactivity tends to increase the ischemia of bowel wall which prolongs the phase of capillary transudation.

8. The Plexiglas window provokes adhesion development and reperitonealization in 20 to 30 days.

9. The evolution of the uncomplicated intraperitoneal fibrinous adhesion lasts approximately 48 to 96 hours. Efforts to shorten this period appear to complicate a natural healing phenomenon with longer periods of adynamic ileus and/or the development of permanent fibrous adhesions.

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A COMPARISON OF THE ANTISECRETORY AND VAGOLYTIC EFFECTS OF THE BELLADONNA ALKALOIDS AND CERTAIN SYNTHETIC PARASYMPATHOLYTIC DRUGS

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OBJECTIONS are often raised to the use of antisecretory drugs during operation because untoward side effects are occasionally observed. The drugs used for this purpose are parasympatholytic substances. Even though atropine has been universally accepted as the drug of choice, one must concede that it is not always efficient and that, at times, it causes undesirable side actions such as tachycardia and flushing. Scopolamine appears to be more efficient for minimizing secretions but is not used by many as the routine preoperative parasympatholytic drug because disorientation occasionally occurs. Besides, it appears to be less effective than atropine as a vagolytic agent. All of this is based upon clinical impressions. Even though the literature on the belladonna alkaloids is voluminous, quantitative measurements and controlled studies of antisecretory effects on man have not been available. Recently a number of new parasympatholytic drugs have been offered as spasmolytic agents to alleviate gastrointestinal spasm. The possibility that these could be of service as antisialogogue and vagolytic agents interested us. In this study we have undertaken the evaluation and comparison of the antisecretory effects of the time-honored belladonna alkaloids and of some of these newer drugs as well. In addition, since these drugs are used for depressing the vagus during surgery, we have studied their vagolytic effects using acceleration of the pulse as an index of such an effect.

The drugs tested were levo-hyoscyamine (Bellafoline, Levsin), atropine, scopolamine, Dibuline [bis (dibutyl-carbonate) of ethyl (2-hydroxyethyl) dimethylammonium] sulfate, Pamine (scopolamine methyl bromide), Antrenyl (phenyl-cyclohexyl-oxyacetic acid diethylaminoethyl bromide), dextrohyoscyamine. The dosages employed of these newer drugs were those recommended by their investigators for their spasmolytic effects. Methantheline (Banthine) was not included in this study because, in a previous study from this department in which the drug was used as an antisecretory agent in anesthetized pediatric patients, hyperthermia and extreme tachycardia were encountered.[1] We cannot share the enthusiasm of Alver and Vanderwood[2] for this compound as a drying agent.

Certain patients with allergic disorders premedicated with parasympatholytic drugs in combination with various antihistaminic drugs appear, at times,

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to have more dryness of the mucous membranes than usual. Many antihistaminics possess some anticholinergic activity and vice versa—many anticholinergic drugs possess some antihistaminic activity. Therefore, the potentiating effects of chlorpheneramine (Chlortrimeton), an antihistaminic, combined with certain of these drugs was also studied. This particular antihistaminic was selected because it appears to possess less of a hypnotic effect than other antihistaminics.

METHOD OF STUDY

This study was performed on unanesthetized adult volunteers. A preliminary summary of the data in this report has been presented elsewhere.[4] The subjects were 189 young male and female volunteers. Each drank several glasses of water one hour prior to the administration of the drugs to assure adequate hydration. Control data concerning pulse, blood pressure, oral temperature, and secretory activity of the salivary and buccal glands were first obtained. Secretory activity was determined by placing 3 previously weighed pledgets of cotton in the mouth, one at the opening of each of Stenson's ducts and one sublingually. The cotton pledgets were made of Webril because of its high absorbent capacity and its ability to be moulded into a desired form and to maintain its shape. This particular technique was selected because it eliminated to a large extent the mechanical stimulation, such as would be encountered if the salivary glands were cannulated, and also took into consideration the secretions of other glands in the mucous membranes. After 5 minutes the pledgets were removed and immediately reweighed to determine the amount of secretions formed. The drug under study was then injected subcutaneously. The pulse rate was determined at 5-minute and blood pressure at 10-minute intervals. After 40 minutes the salivary output was once again determined by introducing a fresh set of weighed cotton pledgets in the same manner described above. The 40-minute waiting period was selected because some drugs required as long as 30 minutes for the drying effect to become established. A figure which the writers have termed "the drying index" is computed by dividing the weight of the secretions after the drug is given into that before it is given. An index of 1 indicates no drying effect. The larger the value of this index the better the drying effect. The body temperature was also again determined at this time. Side actions, such as flushing, nausea, feeling of warmth, dryness of the skin, drowsiness, and so forth, were also noted. The subjects were not told which drugs they were receiving. Saline was used as a control.

RESULTS

Levo-hyoscyamine (0.5 mg.) was found to be the most potent antisecretory agent of the drugs tested. Levo-hyoscyamine is one of the optical isomers present in atropine, the other being dextro-hyoscyamine. Atropine is racemic tropine tropate since it contains equivalent portions of each isomer. We have employed levo-hyoscyamine as an antisecretory drug and as a vagolytic agent since 1951. To our knowledge this was the first time the drug had been used

as an antisecretory drug. The index for levo-hyoscyamine was 14.3. Some acceleration of pulse rat occurred; an average of 27 beats per minute was recorded over the control level.

The most exhaustive study was done on atropine, since it has for many years been considered the standard. Three series using different dosages of atropine were investigated. The first, using a dosage of 0.43 mg. (gr. $\frac{1}{150}$), gave a drying index of 1.5 and no change in the pulse rate when comparison was made with the control level. When the dosage was increased to 0.65 mg. (gr. $\frac{1}{100}$), a drying index of 2.9 was observed and an increase of heart rate of 8 beats per minute was obtained. In the final series on atropine, 1.08 mg. (gr. $\frac{1}{60}$) was administered. The drying index with this dosage was 5.9. An increase in pulse rate of 21 beats per minute was noted.

The drying index of scopolamine (0.5 mg.) was 11.1. It proved to be an excellent substance as far as antisecretory activity is concerned and had practically no effect on pulse rate. The central action of scopolamine is noteworthy. All subjects, as one would anticipate, complained of some drowsiness. It was further noted that none of the subjects reported any amnesic effects. The classic amnesia seen in "twilight sleep" (scopolamine and a narcotic) is probably due to a combined effect of the 2 drugs involved.

Dibutoline (Dibuline) (25 mg.) was found to have only a fair antisecretory action since its index is 1.9. A moderate acceleration of pulse rate was seen (+32). A marked cycloplegic activity lasting 12 to 24 hours was noted in half the subjects receiving this drug.

Pamine (scopolamine methyl bromide) (1.0 mg.) showed an outstanding antisecretory activity second only to levo-hyoscyamine in potency, having an index of 12.5. However, a most pronounced, and at times, disturbing acceleration of pulse rate occurred, the average being 58 beats. In several subjects the pulse rates accelerated to 150 or more. Two of the 17 subjects tested with Pamine developed edema of the face and hands and urticaria. Much smaller doses are necessary when this drug is injected than when used orally. Drowsiness was not observed.

The results using oxyphenonium (Antrenyl) in 1.0 mg. doses were disappointing. We were forced to limit our studies with this drug because of the side actions encountered. It had a somewhat better antisecretory activity (index 4.6) and approximately the same effect on pulse rate as did Dibuline. Of 4 subjects tested with this drug, 3 developed macular rashes of the face and trunk. Two complained of severe, throbbing headache, and one of hesitancy. The increase in pulse rate was found to be marked though not nearly as great as that noted with Pamine. We are unable to share the enthusiasm of Stephen and his coworkers[3] for the drug as an antisialogogue and a vagolytic agent.

The dextro-hyoscyamine* (0.5 mg.) appeared to be almost devoid of antisecretory or other pharmacologic activity, having an index of 1.0 and no effect

*This compound was specially prepared for our use through the courtesy of Sandoz Pharmaceuticals. This compound is not ordinarily found in nature in its pure form.

on pulse rate. This is interesting since this derivative comprises half of a given portion of atropine, the other half being levo-hyoscyamine.

Chlortrimeton (10.0 mg.) showed a drying index of 1.2 and a decrease in pulse rate of 8 beats per minute. We view this decrease of 8 beats per minute with interest but are aware that it may well be due to experimental error. Chlortrimeton combined with atropine or scopolamine produced no significant potentiation or increase of drying effect.

TABLE I

	INCREASE OF PULSE/MIN.	DRYING INDEX	OTHER SIDE EFFECTS
Levo-hyoscyamine (0.5 mg.)	27	14.3	None
Atropine (0.43 mg.) gr. 1/150	0	1.5	None
Atropine (0.65 mg.) gr. 1/100	8	2.9	None
Atropine (10.8 mg.) gr. 1/60	21	5.9	None
Scopolamine (0.5 mg.)	2	11.1	Drowsiness
Dibuline (25 mg.)	32	1.9	Cycloplegia
Pamine (1 mg.)	58	12.5	Urticaria
Antrenyl (1 mg.)	30	4.6	Skin rashes, throbbing of heart
Dextro-hyoscyamine (0.5 mg.)	0	1.0	—
Chlortrimeton (10 mg.)	(−) 8	1.2	—
Saline	0	1.0	—

DISCUSSION

It is worth noting again that the data presented in this report were obtained using unanesthetized volunteers. Are these results valid in anesthetized patients? Obviously it is not possible to use this technique in anesthetized, human subjects. However, conclusions drawn from this study coincide exactly with those drawn from a clinical study made on pediatric patients reported from this department[1] and clinical observations in adults during anesthesia made subsequent to this study. In 579 children, predominately from the otolaryngologic services, premedicated with various anticholinergic drugs, scopolamine proved satisfactory in 90 per cent of the patients, levo-hyoscyamine in 89 per cent, and atropine in only 36 per cent. Skin rashes and hyperthermia were not observed in a series of 1,000 children receiving single doses of atropine subcutaneously.

The fact that the dryness of the mouth of which patients complain preoperatively may be in part due to dehydration from fasting is often overlooked. It is felt that the dosage of the parasympatholytic agent should be increased for hydrated patients, such as those who are being given intravenous fluids. As a specific example, in adults who are in a state of good hydration, no less than 1.0 mg. of atropine or 0.5 mg. of levo-hyoscyamine should be used. As with all other drug therapy, when extremes of age or toxic states and so forth are being dealt with, the dosage scale must be modified.

If we use increase in pulse rate as an indication of peripheral vagolytic activity, it is clear that antisialogogue and vagolytic activity do not necessarily parallel each other. From the foregoing data 2 striking examples of this are seen when the results with scopolamine are compared with those of

Dibuline. Scopolamine gives excellent drying effects with little peripheral vagolytic activity. On the other hand, Dibuline has greater vagolytic activity but is relatively devoid of antisialogogue effects. Levo-hyoscyamine has a greater vagolytic effect than atropine.

CONCLUSIONS

1. Conventional adult dosage of atropine (gr. $1/150$) as a preoperative antisialogogue is inadequate. Larger doses may be used without ill effects. The antisecretory effect of atropine is due largely to the levo-hyoscyamine in the racemic mixture. The dextro-hyoscyamine is devoid of drying effect. The pure levo-hyoscyamine (Bellafoline, Levsin) is more effective than atropine and should supplant atropine as an antisecretory drug.

2. Scopolamine (d-hyoscine) is as effective as an antisialogogue as is levo-hyoscyamine but is less effective as a vagolytic drug. Disorientation and delirium are the exception rather than the rule when this drug is used.

3. In dealing with hydrated patients larger dosages of drying agent are necessary as compared with patients who have been without food or drink for 8 or 10 hours.

4. The belladonna alkaloids are superior to the synthetic spasmolytic drugs in most respects. Scopolamine methyl bromide (Pamine) was nearly as effective as levo-hyoscyamine in 1 mg. subcutaneous doses but caused a marked cardioaccelerator effect and cutaneous manifestation. Antrenyl is relatively ineffective.

5. For supplementation of antisialogogue effect during anesthesia, scopolamine is the drug of choice because of its lack of peripheral (cardioaccelerator) effects. Where the peripheral effect does not matter or is desired levo-hyoscyamine is desirable. Our preferences in dealing with various problems are as follows: scopolamine for infant cardiac patients, patients with impending heart failure, situations in which amnesia is desired, in febrile patients, and thyrotoxic patients; and Levo-hyoscyamine (or equivalent dosage of atropine) for youthful patients, elderly patients, or in patients in whom excessive autonomic reflex activity is anticipated.

Recently Wyant,[5] using the technique of applying suction to a single parotid duct and comparing scopolamine, atropine, and levo-hyoscyamine, has arrived at the same conclusion as we have concerning these 3 drugs.

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URINARY TRACT METASTASES BY CANCERS OF LARGE BOWEL

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THE initial radical surgical procedures for treatment of malignant neoplasms of the large bowel, as well as female reproductive organs, are often inadequate in obtaining a maximum survival rate. Although the tumors at the time of operation may appear well localized without gross metastatic evidence, late postoperative metastases may occur at the site of surgery and in distant organs by hematogenous spread. It may likewise involve the adjacent retroperitoneal space and urinary tract, progressing often to unexpected terminal uremia. Such metastases do occur more often than previously observed by Bacon and Jackson.[2] In a series of 600 autopsies, they observed 5.6 per cent bladder, 3.1 per cent prostatic, 2.5 per cent seminal vesicle, 1.8 per cent urethral, and 0.6 per cent ureteral metastases. In addition, a few lower genitourinary metastases have been reported with involvement of the penis, and at least one to the vulva[17] from a rectal carcinoma, and one to the testes from a colon carcinoma.[3] Likewise, Abeshouse and Goldstein[1] collected 16 cases of colon carcinoma with renal metastases. An additional case reported by Sawyer and Spencer[14] appeared 3 years following the resection of a sigmoid tumor.

To substantiate our clinical impression that urinary metastases occur more often, 75 consecutive autopsies with cancers of the large intestine were reviewed. A significant difference was noted in the incidence of urinary tract involvement and therefore neoplasms were separated into primary colon and primary rectosigmoid tumors. Analysis of 50 rectosigmoid tumors revealed a much higher incidence of metastases to the urinary tract than had been previously suspected. There was no involvement of the urinary tract in 40 per cent of the cases. Sixty per cent showed malignant invasion with 4 per cent renal and 16 per cent ureteral metastases (alone, or with additional involvement of the bladder, prostate, and seminal vesicles) and 40 per cent presented direct extension of the tumor to the bladder, prostate, and seminal vesicles, with approximately one-half of them developing ureteral obstruction at the ureterovesical junction. Twenty-five colon cancer autopsies revealed absence of urinary involvement in 84 per cent of the cases. Of the 16 per cent involved, 4 per cent showed renal involvement by direct extension of a colon-flexure tumor, 4 per cent had ureteral involvement by a direct extension of a cecal tumor, and 8 per cent presented metastases to the bladder or seminal

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vesicles. The great difference between these findings and those previously reported is probably due to the fact that both rectosigmoid and colon carcinomas were considered as one group.

Invasion of the urinary tract occurs in 3 ways: by hematogenous spread to the kidneys, by direct extension of the tumor to the bladder, prostate, seminals, and lowermost ureters (Fig. 1), and by lymphatic spread. The latter in addition may occur by direct invasion of the structures, but more frequently the involved retroperitoneal lymphatic nodes extend into the periureteral fascia and ureteral wall at the brim of the pelvis (Figs. 2 and 3). This produces ureteral stenosis with obstruction to urinary drainage, resulting in slow

Fig. 1.—Tumor mass involving the urinary bladder and both ureteral orifices from an adenocarcinoma of the rectum. Marked bilateral ureteral dilation and pyelonephritis were found at autopsy. (Arrows indicate ureteral lumina sectioned above the stenotic intramural portion.)

progressive hydropyonephrosis and uremia. These lymphatic nodes are represented by the iliac and presacral chains which drain regional lymphatic stations via existing lymphatic intercommunications. By the time the patient has surgery, 56 per cent of the rectosigmoid tumors have metastasized to some of these regional nodes (intermediate or central mesocolic glands). This 56 per cent is an average figure, since different figures range from 47 to 62 per cent.[10, 11] Involvement of these iliac and presacral lymphatic groups has been responsible for diagnostic urographic "medial fixation" of the ureters, noted by Spillane and associates[15] (Fig. 4).

The urinary tract is therefore more readily involved by rectosigmoid neoplasms because of its anatomic proximity, lymphatic intercommunications, and retroperitoneal channels which assume the character of a metastatic "target" area. The retroperitoneal chain is represented by lumboaortic, lower iliac, and presacral groups. Knowledge of lymphatic drainage is necessary for the surgeon who intends to cure cancer by eradicating both the local lesion and the area of possible lymphatic spread (Fig. 5).

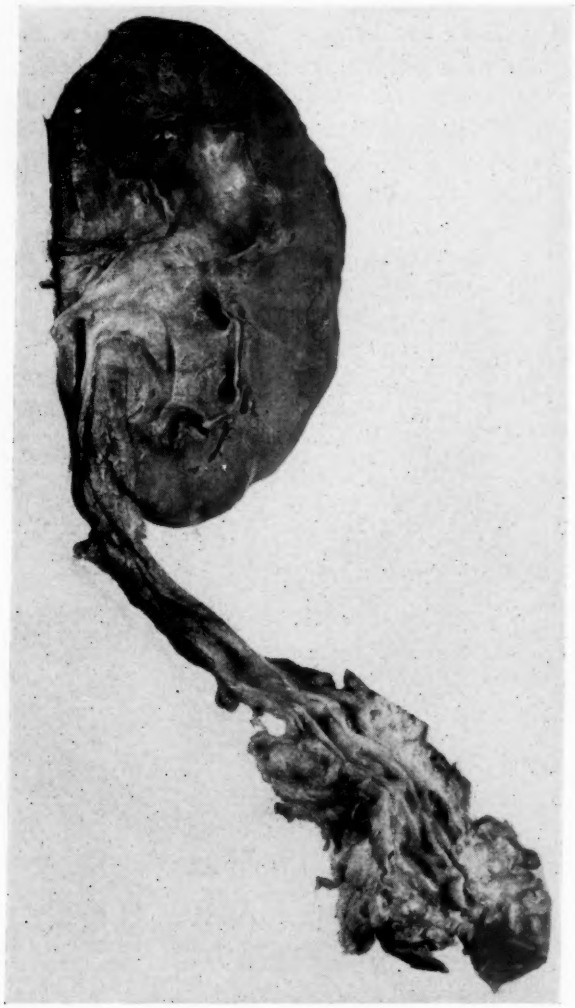

Fig. 2.—Typical stenotic left periureteral metastatic lesion with dilated ureter, hydronephrosis and pyelonephritis above, from a primary adenocarcinoma of the rectum. Autopsy disclosed additional extension of the tumor to the bladder base, both ureteral orifices, and seminal vesicles. Stenosis of the ureter is produced by direct compression without mucosal invasion, which may follow later.

Lymphatic spread of the rectosigmoid carcinoma, the most frequent site of large bowel tumors, has been extensively studied since Miles.[4, 6-11, 13, 16] From the anal canal the drainage is to the inguinal nodes. At the level of the levator ani insertion, the flow is upward to the nodes about the superior hemorrhoidal vessels, laterally along the levator ani muscles to the obturator nodes

Fig. 3.

Fig. 4.

Fig. 3.—Right retrograde urography disclosing hydronephrosis and obstruction of ureter at pelvic brim. Obstruction at the left ureterovesical junction did not permit catheterization.

Fig. 4.—Right retrograde urography demonstrated medial angulation and fixation of the ureter with hydronephrosis.

and the ischiorectal fossa, and then to the iliac nodes. Thus, Miles stressed the removal of the pelvic peritoneum and the levator ani muscles at their attachments. At the mid-rectum and above, the flow follows the superior hemorrhoidal vessels to the nodes about the aortic bifurcation, aorta, and inferior mesenteric vessels. When these stations are blocked, downward retrograde spread may occur. Additional presacral nodes are situated mainly between the posterior rectal wall and concavity of the sacrum, within the adipose tissue of the mesorectum. Particularly above the peritoneal reflection, significant spread may occur along the intramural lymphatic plexus, 7 to 8 cm. from the apparent limits of the neoplastic lesion. Gross evidence of such extension is represented sometimes by the presence of a small granular-like spread over the bases of the appendices epiploicae. The lymphatic flow from the sigmoid, after passing through epicolic, paracolic, and intermediate nodes,

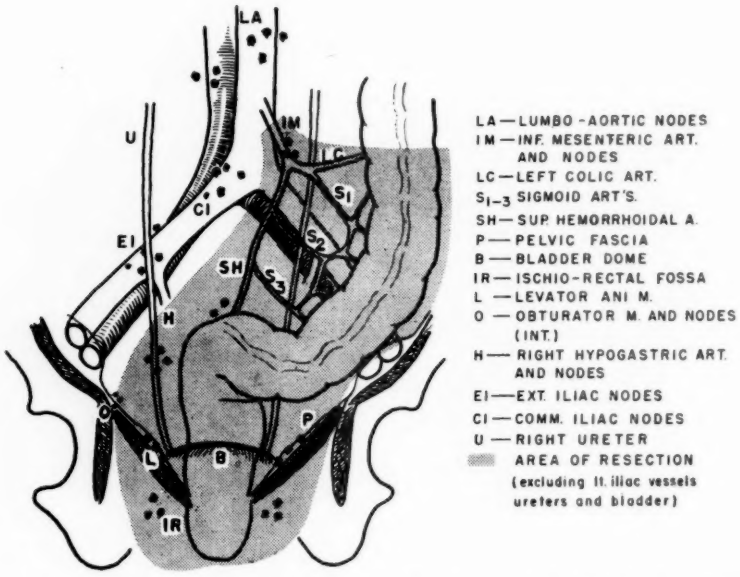

Fig. 5.—Lymphatic stations involved in rectosigmoid cancers and extent of resection for rectal and low sigmoid lesions.

reaches the inferior mesenteric nodes (central stations). It is quite apparent that a more extensive initial effort should be made to remove the primary lesion with its regional lymphatic drainage areas. Only then will urinary metastases be avoided or delayed and the percentage of survival rates increase. It is rather tragic today to conclude that the survival rate remains almost at status quo compared to that of 25 years ago. In certain cases the reluctance to extend further below the lower line of excision and renounce the end-to-end anastomosis of the colon to the lower rectum is another important factor in this consideration. The extreme cleansing procedure in advanced cases advocated by Deddish[5] should be evaluated, although this procedure requires a great technical effort.

Postoperative follow-up is another factor of great importance in obtaining a maximum survival rate. Reinvestigation of the intestinal tract, respiratory tract, and other systems, as well as "second look" laparotomies have

been performed in the hope of detecting and eradicating recurrent lesions. The high percentage of urinary tract involvement found on postoperative examinations of rectosigmoid cancers indicates the advisability of including urographic studies in every follow-up case. Routine urinary tract roentgenograms and blood urea nitrogen determinations once every 6 months are indispensable in detecting possible urinary metastases at a time when urosurgical procedures may still offer something more concrete. Ignoring the urinary tract may lead to a slow, insidious progression of hydropyonephrosis secondary to obstructive uropathy, irreversible parenchymal renal damage, and uremia. The presence of clinical indications or suspicion of urinary tract involvement at any time suggested by symptoms or laboratory findings should require, on the other hand, an immediate investigation including urethrocystoscopy. When a urinary lesion is found too late, after an almost silent and asymptomatic course, and often accidentally, surgical relief is not always feasible because of the complications previously mentioned. Too often the operative site, anastomosis, and so forth are investigated alone in an effort to explain various symptoms. This reluctance to consider study of the urinary tract as a possible solution of the problem has been noted by Krause and Lubert.[12] Equally important is the preoperative intravenous urogram to be used as a postoperative control for comparison studies. Information obtained by intubation of the ureters prior to bowel resection, and simultaneous cystoscopic survey are indispensable for optimal planning of the surgical procedure.

Effective treatment for these metastatic conditions consists of urinary diversion which may be accomplished by a simple, permanent nephrostomy or ileal substitute bladder. Selection of the procedure will depend upon several factors such as the patient's general condition, the local and distant metastatic situation, and the surgeon's philosophy and experience. However, we do believe, in general, that nephrostomy is the best conservative procedure in prolonging the patient's life and in carrying less operative and psychic trauma. The separate ileal loop into which ureters can be implanted is a far better procedure than a wet colostomy or cutaneous ureterostomy because of the difficult postoperative care and ascending infections. On the other hand, ureterosigmoid anastomoses are being obviated in view of the large urinary reabsorption surface with hyperchloremic acidosis.

Urinary tract metastases show a tendency toward bilateral symmetrical involvement with resulting uremia. In the case of a slow progressive, unilateral hydronephrotic atrophy, blood chemistry changes will not be produced as long as the other kidney remains normal. However, since the involvement is bilateral, intravenous urography will reveal either bilateral hydronephrosis or unilateral hydronephrosis with a contralateral nonfunctioning kidney (Fig. 6). When this occurs, retrograde urographic evaluation of the upper urinary tract should be undertaken to decide if an ileal bladder is feasible or to select a diversion via a nephrostomy on the side of better function. Bilateral incapacitating nephrostomies, in addition to a colostomy, do not seem advisable. The colostomy adjustment problem alone is often not satisfactorily obtained.

In more advanced cases, unilateral nephrostomy of the apparently better functioning kidney has been sufficient to return the blood chemistry to normal or close to normal range. Cases of bilateral involvement with one kidney presenting hydronephrotic atrophy should not be considered hopeless since even at this point unilateral nephrostomy of a functioning kidney will assure further prolongation of life. Compensatory hypertrophy of the nephrostomized kidney will continue to manage satisfactorily the metabolic requirements.

The following 2 representative clinical abstracts illustrate a case of an unexpected terminal uremia secondary to urinary tract metastases, and a case in which urinary diversion for such metastases prolonged the life over a year.

Fig. 6.—Intravenous urography discloses poor right renal function with hydronephrosis and hydroureter. A nonfunctioning left kidney is present.

CASE REPORTS

CASE 1.—An abdominoperineal resection for carcinoma of the rectum was performed on this 28-year-old man approximately one year prior to the present hospital admission. An additional finding at time of surgery was polyposis of the colon. Prior to admission the patient had been vomiting for the past 3 weeks, had been anorexic for 1 week, and anuric for the last 2 days. He appeared critically ill with dyspnea, orthopnea, coughing, diaphoresis, and rales in both lungs. The blood urea nitrogen was 180 mg. per cent, serum chloride 76 mEq./L., sodium 139 mEq./L., and potassium 9 mEq./L. Following an attempt of corrective and supportive therapy, the patient expired 12 hours after admission in deep uremia. Autopsy disclosed extension of the recurrent tumor into the bladder, prostate, and seminal vesicles, pelvic and splenic metastases, bilateral hydronephrosis and pyelonephritis, parenchymal degeneration of the kidneys, fibrinous peritonitis, and acute bronchopneumonia.

CASE 2.—The past history of this 59-year-old man disclosed colon polyposis and chronic ulcerative colitis. Following a partial colectomy in 1949, a total colectomy with ileostomy was done in 1950 with additional findings of multiple adenocarcinoma of sigmoid polyps. On admission the patient appeared chronically ill, was anemic, hypertensive, and complained of right lumbar pains. Blood urea nitrogen was 77 and rose to 125 mg. per cent. Intravenous urography disclosed bilaterally nonfunctioning kidneys, and right retrograde urography revealed ureteral obstruction. A right nephrostomy was performed and ureteral obstruction at the pelvic brim noted, with additional hydronephrosis and pyelonephritis. Three weeks after right nephrostomy the blood urea nitrogen dropped to 20 mg. per cent, and following a left nephrostomy reached the normal level of 14 mg. per cent. The urinary drainage was satisfactory and nephrostomy catheters were changed every month on an outpatient basis. Two episodes of acute pyelonephritis were controlled with antibiotics. Fourteen months following the nephrostomies, the patient expired with terminal pulmonary, lumbar, pelvic, ureteral, and bladder metastases, and acute bronchopneumonia.

SUMMARY

Since the present literature is extremely poor in references to metastatic involvement of the urinary tract by cancers of the large intestine, it was our intention to present this problem from a diagnostic and therapeutic point of view. The latter consists of urinary diversion with significant prolongation of the patient's life. Emphasis was placed on lymphatic drainage to illustrate the mode of dissemination of urinary metastases from rectosigmoid tumors. An analysis of 75 autopsies has been presented and findings of 50 cases with carcinoma of the rectosigmoid revealed a 60 per cent incidence of metastatic invasion of the urinary tract. Metastases present a silent course, and urinary obstructions are often discovered unexpectedly, usually associated with uremia. In order to detect such involvement earlier with more successful urosurgical intervention, routine and systemic postoperative urography in rectosigmoid cancers is indispensable. Equally important, preoperative urography and information from preoperative ureteral intubation with simultaneous cystoscopic survey appear necessary for optimal surgical planning.

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INTRAVENOUS ABDOMINAL AORTOGRAPHY

A Preliminary Report

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INTRODUCTION

THE development of translumbar aortography by dos Santos in 1929[2] opened the way for the diagnosis and study of vascular disease of the abdominal aorta, its main branches, and the kidneys. However, the widespread use of this procedure has resulted in a number of serious complications and sometimes death. The complications which have been reported include pain, hemorrhage, superior mesenteric artery thrombosis, embolism, renal insufficiency, paraplegia, hemothorax, chylothorax, pancreatitis, and adrenal necrosis.[1]

Many of these complications are no doubt due to local factors involved in the "blind" translumbar puncture of the aorta. Some others are due to the employment of high concentrations of contrast agents, which have toxic properties for vascular endothelium in the local area of injection. For these reasons, other approaches to the radiologic visualization of the aorta have been investigated. These have included retrograde femoral artery catheterization and forward approaches via the left ventricle, aortic arch, brachial artery, and subclavian artery. Although successful aortograms may be obtained by means of these techniques, the difficulties, risk, and morbidity are still present. In contrast, a venous approach, if feasible, would eliminate all of the local complications mentioned and add no further morbidity or risk to the procedure.

A study of the possibility of intravenous aortography was therefore undertaken. Several developments in radiology in recent years made such an approach seem practical. It was demonstrated as early as 1937[4] that, with a rapid intravenous injection of radiopaque contrast material, the various chambers of the heart and great vessels and even a large portion of the thoracic aorta could be visualized when cardiac physiology was relatively normal. Further refinements of angiocardiography have been made possible with biplane rapid film changers and a variety of rapid injectors.

During studies on angiocardiography, Steinberg[6] noted radiovascular demonstration of the renal parenchyma following the intravenous administration of iodine-containing media. This incidental finding was utilized in the development of a satisfactory technique to produce nephrograms by Weens,[6] in 1947,

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and was refined still further by the use of body-section radiography (nephrotomography) by Evans[3] and Van Velzer.[5] In some of these studies the abdominal aorta was visualized.

It was necessary for these groups to estimate the vein-to-renal artery circulation time of the contrast material. Evans and his group[3] used the Decholin circulation time for this purpose, while Van Velzer and Lanier[5] introduced a method involving the injection of I^{131} which we have adapted, since it is more objective and can be permanently and accurately recorded.

By combining some of the afore-mentioned techniques and adding other refinements to increase the concentration of the opaque material in the aorta, we have been consistently able to visualize the abdominal aorta in a small series of experimental animals and human patients.

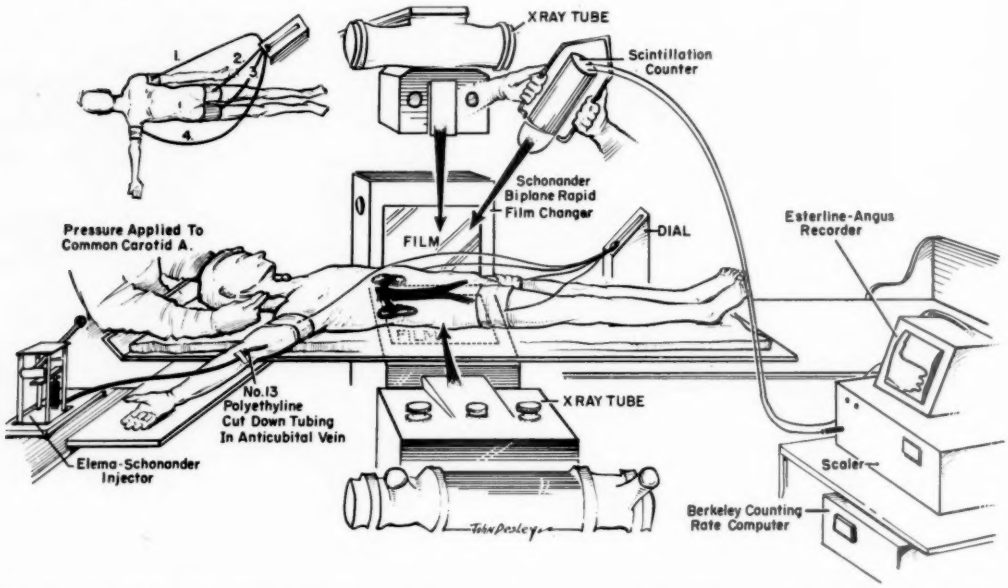

Fig. 1.—A schematic representation of the x-ray room and facilities employed. For further details, see text.

TECHNIQUE

Cut-Down.—Under 1 per cent procaine local anesthesia, the brachial vein is exposed through a cutaneous incision 2 cm. long just proximal to the anticubital space. A No. 320 polyethylene tube (inside diameter = 0.106 inch) is inserted to the level of the subclavian vein. This catheter may then be directly connected to the injector. The cut-down is of value because: (a) it permits the injection of a large amount of contrast material under considerable pressure (and hence during a brief interval of time) which a small vein might not tolerate, (b) it assures the direct entrance of the contrast medium to the central venous pool without the possibility of subcutaneous infiltration, (c) it eliminates venous spasm as a cause of nonvisualization, and (d) it permits the use of compression on all 4 extremities.

Circulation Time Studies.—This is accomplished by layering 25 to 50 μc of I^{131}-labeled Renografin* in front of 45 to 50 c.c. of sterile saline and injecting both materials simultaneously. A collimated scintillation counter is held over the abdominal aorta and the impulses are fed through a scaler and a Berkeley Computing Rate Meter. A tracing is recorded on an Esterline-Angus Recorder and the interval between injection and start of the upslope of activity over the aorta is measured (Fig. 2). The contrast material (1 to 2 c.c.) to be used for the aortograms is added to this circulation time mixture and this acts both to hold the radioactive Renografin in a layer in front of the saline and as a test for possible allergic sensitivity to the dye. The saline volume injected behind the test dose is approximately equal to the volume of contrast to be injected for the aortogram and is necessary to duplicate the circulation time of the contrast material when it is injected.

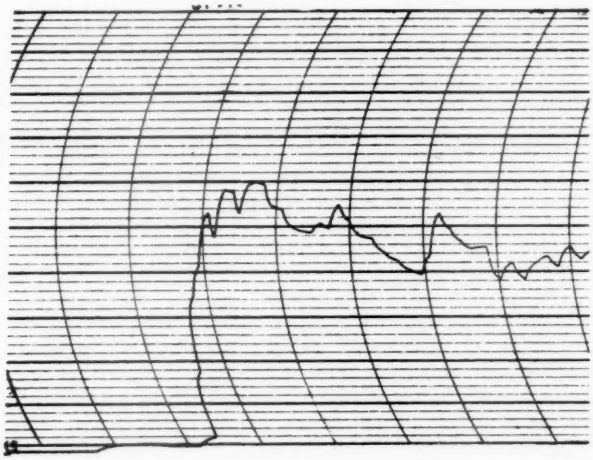

Fig. 2.—Tracing of radioactivity pickup over the abdominal aorta in a normal adult patient after the intravenous injection of radioactive I^{131} Renografin. Note the sharp rise, indicating the sudden appearance of concentrated radioactivity with relatively little dilution, and normal physiology. Vein-to-aorta circulation time averaged 11 seconds in human subjects with norml physiology.

At present we are developing an automatic set-up in which the radioactive material will be layered in front of the contrast, and its detection by the scintillation counter and recording device will automatically start the x-ray exposures.

The Injector.—A lever-type hand injector (Elema-Schonander Co.) is used in these studies. This enables us to make the entire injection of 50 c.c. of contrast material in one to two seconds. It was extremely difficult to obtain satisfactory studies using a simple syringe for injection.

Contrast Material.—We have utilized both Hypaque M 90 per cent and Cardiografin 85 per cent and have found both to be satisfactory. More dilute agents could not be expected to cast a dense enough shadow for these studies.

X-ray Apparatus.—To date, these studies have been performed using a Schonander biplane rapid changer operating at a rate of 1½ to 2 exposures per

*Kindly supplied by E. R. Squibb & Sons, through the Squibb Institute for Medical Research, New Brunswick, N. J.

second. Films are exposed in the frontal and lateral projections simultaneously. The lateral plane offers certain advantages over the frontal in that the aorta is not overlying the spine. However, simplification of equipment seems quite feasible and 2 or 3 exposures in a single plane might give very adequate visualization.

Peripheral Vascular Compression.—Blood pressure cuffs are applied to all 4 extremities and connected to a single bulb and manometer. About one minute prior to the injection, these are pumped to a pressure exceeding the patient's systolic blood pressure by 20 to 30 mm. Hg and kept inflated until after the injection.

Pyelograms.—Routine KUB films are taken 10 minutes following injection to further evaluate renal function and anatomy. Additional films are then taken as needed for routine intravenous pyelography.

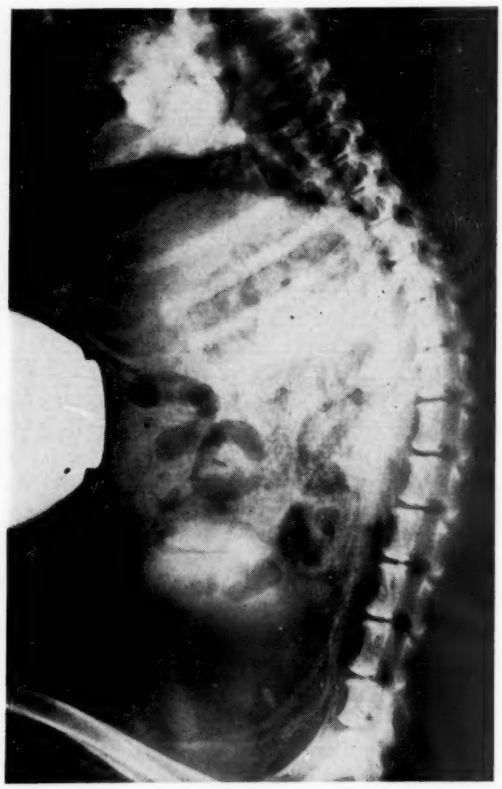

Fig. 3.—Intravenous aortogram in a dog. Note opacification of the major vessels from the heart to the popliteals and scintillation counter in place over the abdominal aorta.

RESULTS

Experimental Animal Work.—Successful radiographic demonstration of the entire thoracoabdominal aorta and its branches down to the popliteal arteries was obtained in 3 dogs (Fig. 3). In addition, visualization of the carotid arteries and their main branches was obtained in 2 dogs when the head and neck region was x-rayed (Fig. 4). These studies were performed without the techniques of peripheral vascular compression and serial biplane radiography and

Fig. 4.—Intravenous carotid angiogram in a dog. Radioactivity was counted over the neck.

Fig. 5.—Intravenous abdominal aortogram in a patient suspected of having an abdominal aneurysm. Note the nephrogram and visualization of the major visceral branches of the aorta.

indicate to us that simplification of our present technique for clinical cases may be possible. Doses of 0.7 c.c. per kilogram of 90 per cent Hypaque were used for these studies.

Clinical Results.—To date, successful visualization of the abdominal aorta has been obtained in 12 consecutive clinical cases (Fig. 5). Several of these patients were over 50 years old and had considerable arteriosclerotic disease. While the aorta and iliacs were visualized in all of these cases, the degree of opacity and contrast varied considerably, depending upon the status of the cardiovascular system of the individual patient. In those patients with occlusive arteriosclerosis, the circulation time to the abdominal aorta was considerably longer, as demonstrated by the radioactive circulation time studies, and there was more time for dilution of the contrast material. We have not examined any patients with congestive heart failure or atrial fibrillation to date. It may be more difficult to visualize the aorta in these individuals. It may become necessary to advance the venous catheter into the right ventricle or pulmonary artery in such cases to secure satisfactory visualization of the arterial tree.

DISCUSSION

The development of an intravenous technique for the visualization of the aorta and its main arterial branches will be useful in the diagnosis of a large number of vascular and renal conditions. It should supplant the translumbar method for the diagnosis of occlusive and aneurysmal disease of the abdominal aorta and its branches because it eliminates all of the complications due to direct aortic puncture. In addition, it may be applied equally well to the study of the thoracic aorta for aneurysm, coarctation, and occlusion. Other suggested uses, which are being evaluated at present, include the diagnosis of superior mesenteric artery thrombosis, lesions of the carotid artery and its branches (particularly internal carotid artery thrombosis), and certain cerebrovascular lesions, the study of renal disease (as a routine scanning test for all hypertensives), follow-up study of patients undergoing vascular surgery, and the study of experimental operative procedures in the animal laboratory.

As these studies progress, it is hoped that the technique can be simplified in some respects. With increased experience in interpreting the circulation time of I^{131} in patients under a number of conditions, it may be possible presently to reduce considerably the number of films required. In addition, the development of more concentrated and less toxic radiopaque materials should extend the usefulness of the method.

SUMMARY

A new technique for intravenous abdominal aortography has been developed for use in both the experimental animal and the clinical patient. It involves the use of a polyethylene cut-down tube in the brachial vein, I^{131} circulation time studies, peripheral vascular occlusion, a hand injector, and a rapid-changing biplane x-ray apparatus. The possibilities for the use of this technique in studying vascular and renal lesions have been discussed.

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SURGICAL EXPOSURE OF THE DISTAL POPLITEAL ARTERY

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RECENT advances in vascular surgery demand frequent exposure of the popliteal artery. The proximal popliteal artery can readily be exposed by an incision in the lower medial thigh, separating the sartorius muscle from the vastus medialis muscle. In many cases, the proximal half of the popliteal artery is occluded, but the distal portion is sufficiently patent to permit anastomosis with an arterial graft. It is necessary to turn the patient to the near-prone position to gain exposure of the distal popliteal artery when one uses the posterior popliteal fossa incision.[1, 4-8] Since both the anterior and posterior surfaces of the leg must be exposed, sterile draping becomes more difficult and a serious problem exists when an abdominal incision is present for the insertion of a graft from the aorta to the distal popliteal artery. Under these conditions, the medial upper calf approach to the distal popliteal artery has proved to be advantageous. This approach is probably being used independently by some surgeons, but the technique is not well known and has not been described in the American literature at the time of this writing.

TECHNIQUE

With the leg externally rotated and the knee flexed approximately 60 degrees, an 8 cm. incision is made posterior and parallel to the posterior edge of the tibia just below the medial tibial condyle. The deep fascia is incised and this permits retraction of the medial head of the gastrocnemius muscle from the tibia with ease, exposing the soleus muscle. The popliteal vein now comes into view lying along the edge of the soleus muscle. Retraction of the popliteal vein exposes the popliteal artery. At this level, the anterior tibial artery branches from the popliteal artery which is described by Gray[2] as the popliteal artery bifurcation (Fig. 1). The soleus muscle covers the artery below this point, and if it is desirable to expose more of the artery, this exposure can be readily obtained by separating the soleus muscle from its tibial origin for a short distance (approximately 3 cm.). The anterior tibial artery is usually small and its general relationship suggests it should be considered as a branch of the popliteal artery. The latter continues its course for 2 to 5 cm. where it divides into the posterior tibial and peroneal arteries,[3] and for surgical purposes this division should be considered the popliteal artery bifurcation since this is the lowest level where an arterial anastomosis can be successfully accomplished in our hands. By traction on the popliteal artery, ample exposure

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is obtained for an end-to-side anastomosis which is usually preferable at this level. After the end-to-side anastomosis is accomplished, an incision is made for exposure of the upper popliteal artery in the lower medial thigh, and a long, curved hemostat is bluntly passed from the thigh incision through the popliteal fossa and under the medial head of the gastrocnemius muscle to the lower operative site where the arterial graft is grasped and easily pulled through this tunnel to the upper incision. It is not necessary to divide the gastrocnemius muscle. Next, the graft may be tunneled to a groin incision or to an abdominal incision through the femoral canal, as indicated. Closure of the wound is accomplished by approximating the deep fascia and skin with fine silk.

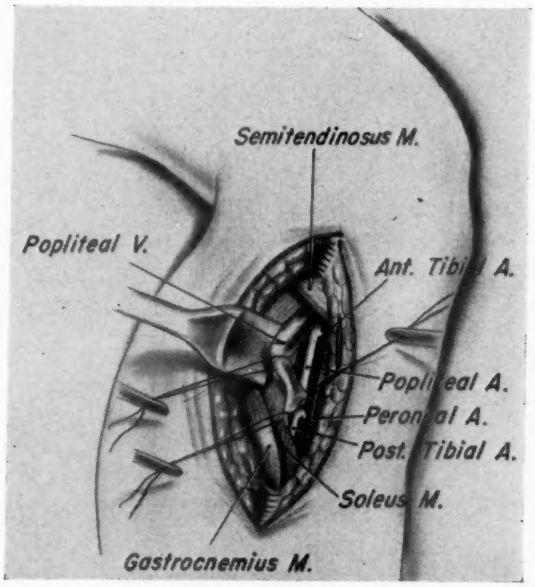

Fig. 1.—Schematic drawing of the anatomy of the medial calf approach to the popliteal artery bifurcation.

CASE REPORT

History.—A 65-year-old white man was admitted July 15, 1957, to the Veterans Administration Medical Teaching Group Hospital, with a chief complaint of intermittent claudication in both legs precipitated by walking 20 yards.

Physical Examination.—The patient was a thin, elderly, white man who did not appear acutely ill and who had no complaints at bed rest. Positive physical findings were confined to the vascular system. Faint arterial pulsations could be felt in the common femoral arteries bilaterally. No pulses could be palpated below this level.

Laboratory Findings.—Laboratory findings were essentially normal.

Course in the Hospital.—Clinical impression on admission was arteriosclerosis obliterans of the aortic bifurcation. A translumbar aortogram was performed and revealed marked narrowing of the aortic bifurcation with a thin trickle of dye visualizing both iliac arteries. Considering the extensive arterial disease of the abdominal aorta and iliac arteries, we assumed that the distal arterial tree of the legs must be open because the circulation in the legs appeared satisfactory at rest. At operation with the patient under endotracheal anesthesia, the abdomen and legs were prepared and draped. Both common femoral arteries were

exposed through short incisions and bilateral femoral arteriograms were performed by injecting 20 c.c. of 30 per cent sodium acetrizoate (Urokon) into each profunda femoral artery. Roentgenogram revealed complete occlusion of both superficial femoral and upper popliteal arteries, but the distal portion of the popliteal arteries appeared normal. A freeze-dried aortic bifurcation homograft was prepared to reach from the mid-abdominal aorta to

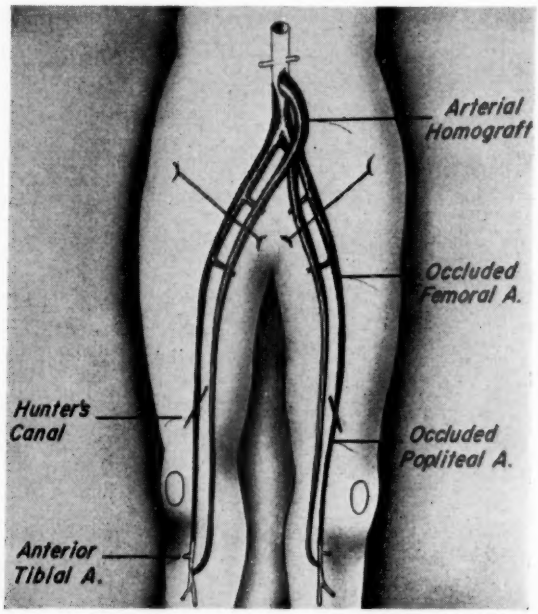

Fig. 2.—Schematic drawing of arterial graft from abdominal aorta to the distal popliteal artery in patient with extensive arteriosclerosis obliterans.

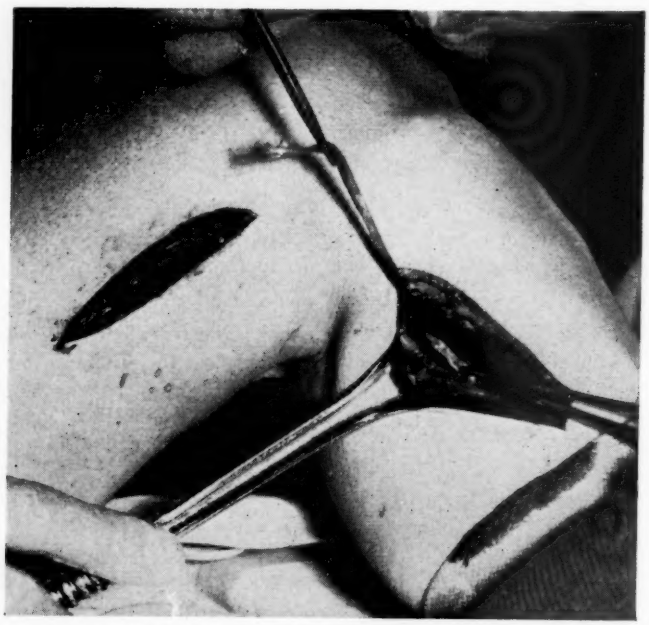

Fig. 3.—Photograph reveals incisions for exposure of the popliteal artery. Bifurcation of popliteal artery can be seen in lower incision.

the distal popliteal arteries. End-to-side anastomoses were performed between the graft and the mid-abdominal aorta above and to the distal popliteal arteries below (Fig. 2). Bilateral lumbar sympathectomies were performed. Postoperatively, the pedal pulses were palpable in both feet and recovery was uneventful. Follow-up examination 6 months after surgery revealed that the patient could walk one mile without symptoms.

COMMENT

We have used this medial upper calf approach to the distal popliteal artery on 25 occasions for the insertion of a bypass arterial graft and on 3 occasions for embolectomy. Initially, we believed that the cases requiring anastomosis to the mid-portion of the popliteal artery could not be handled without turning the patient or cutting the medial head of the gastrocnemius muscle. However, our experience indicates that the entire popliteal artery can be readily exposed without cutting any of the gastrocnemius muscle, utilizing the 2 incisions shown in Fig. 3. It is necessary in exposing the lowest usable portion of the popliteal artery to cut a few of the fibers of the soleus muscle. This approach was found to be satisfactory, simple, and timesaving, it does not require cumbersome turning for the lower grafting, and, in our opinion, it is essential when grafting is needed from the abdominal aorta to the distal popliteal artery (see case report).

SUMMARY

1. The technique for surgical exposure of the distal popliteal artery by the medial calf approach is described.

2. The advantages of this procedure are stated.

3. A case history which demonstrates the use of this incision is briefly described.

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THE USE OF STORED CUTANEOUS AUTOGRAFTS IN WOUND TREATMENT

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ALEXIS Carrel,[10] in 1912, gave us the basis for the modern methods for the preservation of skin. Most of the subsequent clinical work recorded in the literature is concerned with the storage of skin for homotransplantation. In 1925, when hemostasis was a problem in split-thickness autografting, Coller[12] reported a technique in which the application of cutaneous autografts was delayed for 6 hours after their removal. Although the storage of autogenous skin for longer periods was reported clinically in 1945,[24, 33] its use did not become widespread as a practical procedure. Since then, methods of storing skin in a viable state have been greatly improved.

An initial graft of split-thickness autogenous skin does not always "take" successfully. If a large denuded defect persists, the epithelial edges which proliferate across the granulating bed form an inferior protective surface or fail to completely close the defect. Pinch grafts used to cover such defects also result in unsatisfactory epithelization. The reapplication of continuous split-thickness skin is the most effective method of obtaining satisfactory coverage. It is possible to accomplish this without subjecting the patient to another operating room procedure by the use of stored cutaneous autografts obtained at the time of the initial operation. This is a report of our experiences with such a method.

PROCUREMENT

The skin is procured from the patient with a standard dermatome during the initial grafting procedure. Approximately 50 per cent more skin than that required to cover the lesion is removed from the donor site. The excess skin is then stored in the skin bank refrigerator and is available to the surgeon if the grafting procedure must be repeated.

STORAGE

Sterile, 4 ounce, widemouthed jars are used to store the skin. A list of instructions (as shown below) is placed in the jar before sterilization so that it is available to the surgeon and the nurse during the procedure.

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METHOD FOR STORAGE OF SKIN AUTOGRAFTS*

1. Obtain one-third to one-half more split-thickness skin than is required to cover defects.
2. Place cut surfaces together by folding specimen once.
3. Place skin on 4 by 4 sponge that has been moistened with Hartman's solution.
4. Roll sponge containing tissue and place in a sterile glass jar, available as "skin bank jars" in the supply room.
5. Label jar with patient's name, registration number, and date.
6. Add 2 ounces of the "skin bank fluid," which is kept in an operating room refrigerator, to the storage jar and seal with one inch tape. Place jar containing specimen in the operating room refrigerator immediately.

The refrigerator is maintained at approximately 4° C. Since the storage medium is kept in the refrigerator, it is always at the proper temperature.

A standard preservative medium used by others[1, 17, 23] for storing skin has been altered to meet the needs of this technique. This "skin bank fluid" consists of the following: (1) Hank's tissue culture reagents,[17] (2) plasma (blood type A B+)—20 per cent by volume, and (3) neomycin, 500 mcg. per milliliter.

The Hank's medium is prepared by our hospital pharmacist. The plasma is separated from outdated whole blood and is obtained from the blood bank.

APPLICATION

The stored skin is applied in essentially the same manner as is fresh autogenous skin. The local lesion is prepared preoperatively in the usual manner; débridement and moist compresses are employed as needed. The procedure is adapted to the ward treatment room, eliminating the necessity for taking the patient to the operating room.

The following sterile items are placed on a large table:

4 sterile towels	2 sterile sheets
4 by 8 dressings—3 packages	4 by 4 dressings—3 packages
Cotton balls (25-50)	2 basins
4 hemostats	2 forceps
1 scissors	Xeroform gauze
Needle holder	6 towel clips
Scalpel	

5-0 chromic gut sutures with Atraumatic needles attached.

The following supplies should also be available for use during the procedure:

1,000 ml. Ringers solution	Phisohex
Elastoplast	Ace bandage
Sterile gown	Gloves
Caps and masks	Tincture benzoin

The following method has been used to prepare the recipient site with minimal discomfort to the patient at the time of application. The patient is given a combination of a narcotic and a hypnotic one hour before the procedure. He

*Equipment and procedures are listed in detail to provide a convenient reference for nurses or laboratory personnel who might be called upon to carry out these suggestions.

TABLE I

AGE	SEX	LESION	PER CENT TAKE IN FIRST AUTO-GRAFTING	PER CENT TAKE IN STORED AUTO-GRAFTING	STORAGE PERIOD (DAYS)	THICKNESS OF SKIN STORED (INCH)	SIZE OF STORED GRAFT APPLIED (CM.)	BACTERIA REPORT OF STORAGE FLUID	NEED FOR FUTURE GRAFTING	FOLLOW-UP PERIOD WITHOUT BREAKDOWN (MONTHS)
2 mo.	M	Infectious slough	0	80	11	.012	1½ × 7	Neg.	No	1
51 yr.	F	Stasic ulcer	50	70	12	.015+	5 × 6	Neg.	No	1
25 yr.	F	Avulsion	60	100	18	.015	4 × 6	Neg.	No	1
68 yr.	F	Postoperative mastectomy; skin flap slough	Not done	50	23	.015	6 × 20	Neg.	No	3
38 yr.	M	Excision melanoblastoma	0	0	13	.030	5 × 5	Neg.	No	3
61 yr.	M	Infectious slough	60	100	13	.015	3 × 3 1 × 7	Neg.	No	1
75 yr.	F	Burn	Not done	80	8	.015	5 × 3 7 × 2	Neg.	No	1
52 yr.	M	Burn	60	50	11	.015	6 × 4	Neg.	No	8
4 yr.	M	Burn	40	60	10	.020	4 × 10	Neg.	Yes	–
6 yr.	M	Burn	70	80	8	.015	6 pieces 1 × 3	Neg.	No	2
7 yr.	F	Burn	80	50	12	.015	4 pieces 2 × 3	Neg.	No	2
38 yr.*	M (1)	Burn	Not done	75	8	.015	4 × 6	Neg.	No	4
38 yr.	M (2)	Burn	Not done	70	21	.012	4 × 6	Neg.	No	4
38 yr.	M (3)	Burn	Not done	90	7	.015	5 × 8.5	*Pseudomonas*	No	4
38 yr.	M (4)	Burn	Not done	50	13	.010	5 × 5	*Pseudomonas*	No	4
9 yr.*	F (1)	Burn	Not done	100	10	.015	4 × 5	Neg.	No	6
9 yr.	F (2)	Burn	Not done	100	10	.015	6 × 6	Neg.	No	5
9 yr.	F (3)	Burn	80	50	17	.015	Multiple 3 cm. dia.	Neg.	No	5

*Two cases mentioned in text.

is brought to the treatment room on a mobile stretcher which serves as the operating table. Sterile technique is used for the entire procedure; the defect is washed with Phisohex solution and gentle débridement is done if necessary. The wound is carefully rinsed with Hartman's solution. The field is then draped with towels and sheets. The granulation tissue on the surface is abraded with dry gauze to promote surface oozing, and the scalpel blade is used to trim off the high granulations. Moist dressings are applied to the surface for 3 to 5 minutes to achieve hemostasis. During this period, the autogenous skin is removed from the storage jar. It is not rinsed but is placed directly over the defect and trimmed to fit. Excess skin is returned to the skin bank jar for further storage. A sample of the preservative medium is submitted to the bacteriology laboratory for cultures prior to the application.

If the lesion is on an extremity, the graft is not usually sewed into position. If sutures are necessary, 5-0 chromic catgut with attached Atraumatic needle is preferred. Such sutures, placed within 3 mm. of the wound edge, cause little or no discomfort to the patient. Local anesthesia may be used but is usually not necessary. A single thickness of well-wiped Xeroform gauze is applied over the graft. Cotton balls soaked in Hartman's solution are applied over the gauze to provide even pressure. An occlusive dressing reinforced by an elastic type of bandage is then applied. The use of tincture of benzoin to protect the skin prior to the application of tight adhesive tape dressings is recommended. When the lesion is near a joint, a light cylindrical cast is applied. The dressing is allowed to remain in place for approximately 7 days, unless the clinical course indicates earlier removal. Patients may be allowed to go home during this interval.

The graft may be applied in approximately 30 minutes, depending to some extent upon the surgeon's experience. A trained assistant is not necessary; the assistance provided by a nurse's aide has been found to be satisfactory.

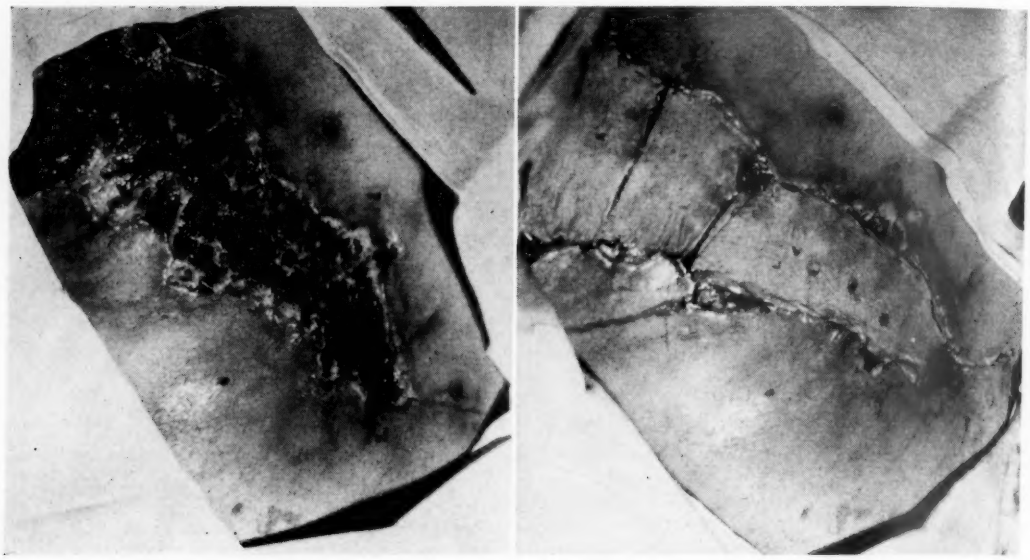
RESULTS

Results are summarized in Table I.

Eighteen stored cutaneous autografts were applied to 13 patients during a 6-month period. The ages of the patients ranged from 2 months to 75 years. Although most of the lesions treated were burns, other types of wounds were also successfully grafted.

In 8 grafts, fresh autogenous skin had not been previously applied. When stored skin was applied, the percentage of "take" ranged from 50 to 100. In the other 10 grafts, stored skin was used because the original grafting had not been fully successful. In this group, there was complete failure in one case, probably because in this instance the skin segment was too thick. It was noted that the percentage of "take" of the stored autograft was greater than that of the fresh autograft in 6 of 10 cases. This would seem to indicate that the viability of stored skin is maintained clinically.

Skin stored from 7 to 23 days remained viable. In one case there was contamination of the storage medium with *Pseudomonas* organisms; however, the skin remained viable and "took" in each of 2 different applications without complications.



A. *B.*

C.

Fig. 1.—In April, 1957, a right radical mastectomy was performed for carcinoma of the breast in a 68-year-old woman. At the time of the procedure the skin flaps were approximated without tension. Although primary healing was anticipated without grafts, split-thickness skin was taken from the left thigh and stored in the skin bank as a precautionary measure. Partial necrosis of the full-thickness flaps occurred, leaving a defect approximately 6 by 16 cm. (*A*). The patient's split-thickness skin, stored for 23 days, was applied in the ward treatment room (*B*) by the method described. A 50 per cent take resulted, establishing islands and bridges across the defect. The patient was discharged to home care and returned 4 weeks later with the wound closed (*C*).

In 2 cases (Table I), small autografts were saved and stored at the time of initial partial autografting of large burn areas. These stored autografts were reapplied in the operating room at the time of the next grafting procedure. At the final autografting procedure for one of these patients, skin was stored and later used to cover the areas that did not take. This was done in the ward treatment room as indicated.

Of the 12 stored autografts applied in the ward treatment room as a definitive procedure, one provided inadequate coverage, and in this patient further autografting was necessary. The follow-up period for the other patients is short to date, but it has been noted that the sites covered by stored autografts are indistinguishable from those covered by fresh autografts.

From this group of patients, a total of 47 autografts were stored. The 29 that were not needed were either sent to the laboratory for tissue survival and bacteriology studies or, if the segments were large enough, they were transferred to the skin homograft bank.

The storage period for the 29 specimens varied from 1 to 3 months. Microscopic sections were made in each case, and viable skin was reported in the older specimens. Bacteriologic cultures were negative in 21 of the specimens. Of the 8 contaminated specimens, 4 contained nonpathogenic mold. The remaining 4 contained bacteria, *Pseudomonas* in 2 instances and nonpathogenic organisms in the other 2. All the contaminated specimens, those in the series of reapplied grafts as well as those not reapplied, were from the same patient.

SUMMARY

A bank for cutaneous autografts can be very useful to the surgeon. A technique for using preserved autogenous partial-thickness skin in grafting procedures has been developed at the University of Michigan Hospital. The method is adaptable to hospitals of all sizes.

In addition to its use in the treatment of burns and the lesions herein described, this technique is applicable to other types of wounds as well. In patients with wounds resulting from trauma which cannot be wisely closed or grafted primarily, skin for storage may be taken while the patient is anesthetized for initial débridement.

Eighteen successive cases are reported in which stored autografts were reapplied after a period varying from 7 to 23 days.

For the procedure, a calculated amount of surplus skin is removed at the time of an initial split-thickness grafting procedure and is stored in a preservative medium at 4° C. In the event of failure of the original graft, the stored autogenous skin is applied at a later time. The procedure can be carried out in the ward treatment room, obviating the need for general anesthesia and for operating room time and space. The patient is also spared the pain involved in the creation of a second donor site. The period of hospitalization is decreased. The stored skin that is not used by the patient, as in the case of a 100 per cent initial "take," is made available for storage in the homograft bank for subsequent use in other patients.

We wish to express our appreciation to Miss Joan Wilhelm, B.S., M.S., who has been responsible for the laboratory studies.

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USE OF AUTOGRAFTS TO BRIDGE DEFECTS IN ARTERIES OF CORONARY SIZE

An Experimental Study

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PURPOSE

IT IS generally recognized that the autogenous arterial graft at present has the most promise as a substitute for a diseased arterial segment. In the use of such grafts there must be no loss of function of the part or parts of the body supplied by the sacrificed vessel. In the majority of cases this will mean an artery of small caliber.

The clinical usefulness of such vessels at present is extremely limited. In the future the use of autogenous grafts to bridge defects in small arteries may be of importance. If a graft of this size can remain patent and functioning, resection of an occluded coronary artery and replacement with a graft would be possible.

The purpose of this study was to determine the ultimate function and survival of autogenous arterial grafts of small diameter following end-to-end anastomosis. The literature is contradictory as to the fate of such grafts. To our knowledge there has been no investigation that indicates the fate of autogenous arterial grafts with an average outside diameter of 3 mm.

HISTORY

The first successful use of an autogenous arterial graft was reported in 1896 by Jaboulay and Briau.[6] They crossed the carotid circulations from one side of the neck to the other in the dog and used an excised segment of artery as a graft. In 1903 Höpfner[5] removed a segment of a dog's common carotid artery and anastomosed it with the cut ends of one of the femoral arteries, from which a segment of similar diameter and length had been removed. Examination after 2 months revealed a smooth intima with but little constriction. Guthrie[4] reported several cases in which he used autogenous carotid artery and venous grafts with satisfactory results. Stich and Zoeppritz[13] in 1909

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observed proliferation of the intimal layer in autogenous grafts which remained patent as long as 14 days. Yamanoüchi[15] could find no alteration in implanted autografts and his findings were corroborated by Lexer.[7] He stated that after several months to a year the normal histologic appearance persisted. Neuhof[10] expressed the belief that autografts underwent a gradual fibrous replacement.

In 1951 Miller and his associates[8] reported 5 cases in which they used autografts measuring 1.8 to 3.5 cm. in length with outside diameters of 3 to 4.5 mm. in the hindlegs of dogs. All 5 grafts remained functioning and patent when the animals were sacrificed 16 days to 12½ months after grafting. They persisted as viable segments of artery with spotty intimal thickening.

Parsons and associates[11] reported successful results in 7 of 8 aortic autografts in dogs. The patent grafts showed no morphologic abnormalities except for an occasional thickening of the intima when observed up to 9 months.

METHOD

Initially the average outside diameter of adult human coronary arteries was determined. As a point of reference, the proximal 3 cm. of the anterior descending coronary artery was measured. Ten adult hearts, chosen at random, that were preserved in formalin were used. At a point 1 cm. from the circumflex coronary artery the average outside diameter of the anterior descending artery measured 4.2 mm. The minimum was 3.5 mm. and the maximum, 5.0 mm. At a point 3 cm. from the circumflex, the outside diameter of the anterior descending branch averaged 3.8 mm. The minimum was 3.2 mm. and the maximum, 4.5 mm.

The common carotid arteries of dogs weighing between 14 and 20 Kg. were found to have outside diameters less than the minimal range of adult coronary arteries in their proximal 4 cm. For this study 20 mongrel dogs were used.

A midline vertical incision in the neck was made and dissection was carried down to expose both carotid arteries. The carotid sheaths were incised. A segment 2 to 3 cm. in length of the left carotid artery was removed and the proximal and distal ends ligated. The right carotid artery was then dissected from the vagus nerve. Glover vascular clamps were placed proximally and distally and a segment of the artery was removed and discarded. The outside diameter of the segment of the left carotid artery was measured and the adventitia was removed from the ends of the vessels for a distance of 4 mm. The anastomosis was made using 5-0 silk with 3 equidistant stay sutures and a running everting mattress suture as introduced by Clermont[2] and Dorrance.[3] A continuous over-and-over suture was used for the first 2 anastomoses. Bleeding from the suture line was controlled in the majority of cases simply by packing for 5 minutes. An additional suture was necessary in a few cases. No bleeding was noted postoperatively.

The grafts were observed for functional and histologic results between 12 and 66 days after implantation at which time they were removed and placed in formalin for 24 hours. The grafts were then imbedded in paraffin

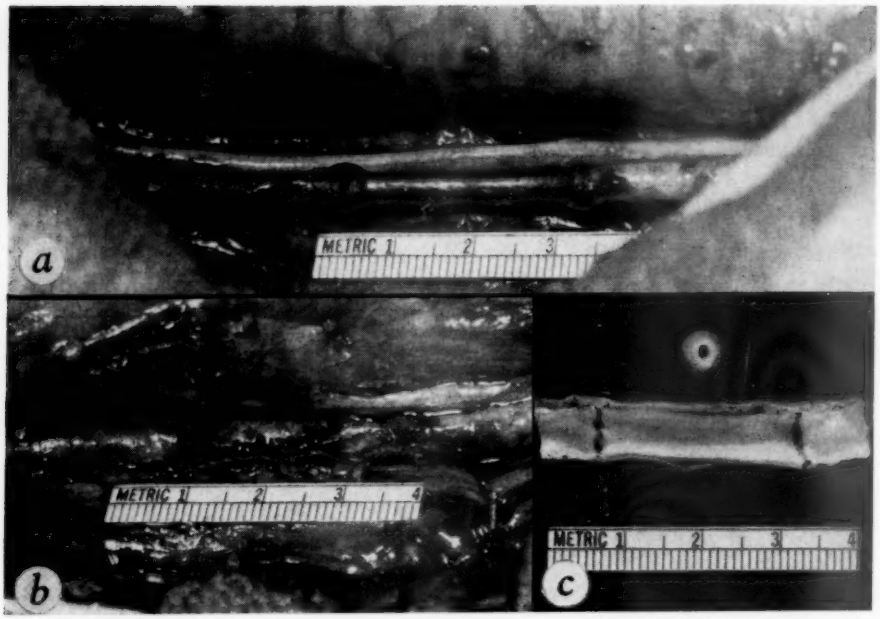

Fig. 1.—*a*, Graft at completion of anastomosis. *b*, Graft in situ after 44 days. A periadventitial fibrous reaction is evident. *c*, Opened graft with cross section of vessel above. Inner surface of the graft is identical with that of the host vessel.

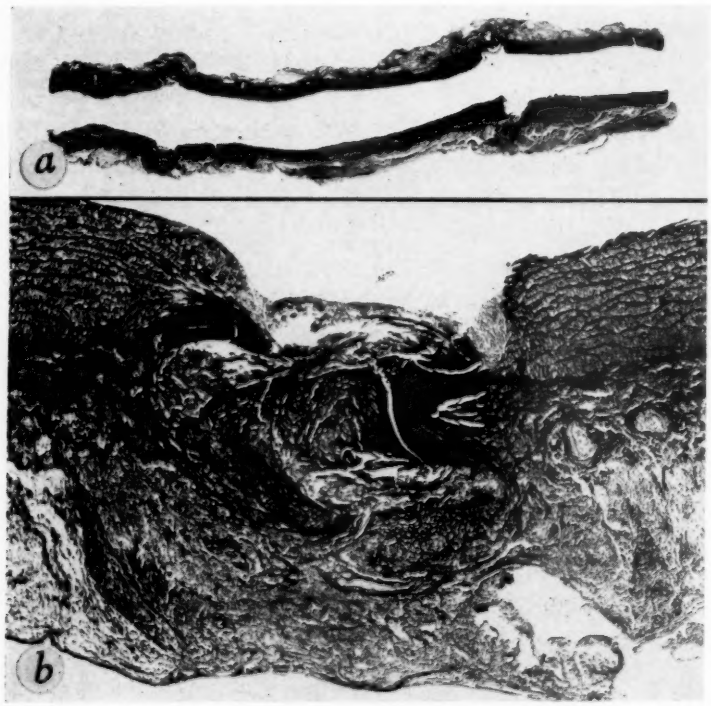

Fig. 2.—Same dog as that represented in Fig. 1. Sections stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain. *a*, Graft and host vessel. There is eversion at the anastomosis with no constriction (×2). *b*, One anastomotic site. The typical adventitial cap and minimal foreign-body reaction in the intima over the suture line are evident. Differences between the graft and the host vessel cannot be detected histologically (×30).

and longitudinal sections were made for histologic study. Sections were stained with hematoxylin and eosin and duplicates were stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain.

RESULTS

Owing to the exact duplication of results in the patent grafts, we feel that a discussion of each individual case would be only a matter of repetition. Hence, we shall discuss the clinical and histologic characteristics of the patent vessels as a group and shall review the 4 failures in more detail.

The grafts were examined 12 to 66 days after their implantation. One animal died 12 days postoperatively of fulminating pneumonia. The graft was patent and histologic sections showed no abnormality. In this series of 20 animals 16 of the grafts remained patent and there was no histologic or macroscopic evidence of any abnormality. There was no constriction or dilatation at the site of anastomosis in any of these vessels.

The average outside diameter of the grafts was 3.04 mm. and the inside diameter, 1.6 mm. Fig. 1 shows the graft immediately after completion of the anastomosis (*a*), the vessel at the time of removal of the graft (*b*), and the smooth intimal surface and sites of anastomoses (*c*). The cross section of the vessel in Fig. 1, *c* portrays vividly the size of the grafts used.

All of the patent grafts remained as apparent viable segments of the common carotid artery. Fig. 2 illustrates this. The everting type of anastomosis is clearly demonstrated. Present at the suture line is an adventitial cap which includes foreign-body giant cells, macrophages, fibroblasts, and dense collagen fibers. There is no intimal thickening aside from the foreign-body reaction at the suture line. The elastic laminae appear alike throughout the graft and host vessel.

Four of the grafts had thrombosis throughout at the time of removal. There is no obvious explanation for the first instance of thrombosis other than the fact that it was the second graft in the series. The second of these was found to be too long at the initial operation. It was necessary to excise the proximal anastomosis and reanastomose the graft with the host vessel, thus doubling the occlusion time. The third instance of thrombosis was the result of a technical error. A mattress suture was used for hemostasis at the peripheral anastomosis and when this was tied down it narrowed the lumen to such a degree that thrombosis occurred immediately. The clot was massaged out of the vessel and only feeble pulsations were present at the time of closure. There is no apparent explanation for the fourth failure. Of the 4 failures 2 were among the first 4 grafting procedures done in this study. There were no failures in the last 10 animals. The average outside diameter of the grafts in these 10 animals was 2.8 mm. The smallest was 2.6 mm. and the largest, 3.0 mm.

COMMENT

The arterial autograft appears to be a satisfactory graft. There have been reports of fibrous replacement and intimal thickening of autografts, but within our period of observation of such grafts this study does not corroborate

these views. We have found, as have others, that the normal histologic characteristics persist in autografts. It is the only viable graft that we have for use at present. If there is one outstanding characteristic it is the viability which makes it so suitable for work with small arteries. The minimal reaction at the suture line does not lead to narrowing of the vessel.

The results with homografts as substitutes for vessels nearing this size have been disappointing. Williamson and Mann[14] reported using carotid homografts in 6 animals. They used 6 venous and 6 arterial grafts in mongrel dogs. Only one graft, an arterial one, functioned satisfactorily. Moore and his associates[9] in a study with freeze-dried and alcohol-preserved homografts of carotid artery reported a 55 per cent over-all success. Callow and Welch[1] had successful results with fresh homografts in 10 of 12 grafts in femoral arteries of dogs. Miller and his associates[8] reported defects present in more than 50 per cent of homografts used in the femoral artery of dogs. Discoloration of the graft and roughening of the intimal surface were the most common defects noted. The majority of these grafts remained patent and functioning after an initial 2-week period.

The homograft does not remain as a viable segment of artery. The major pathologic changes are well documented. The graft maintains a fiber framework and it is reinforced by the ingrowth of periarterial fibrous tissue of the host.

Various types of anastomoses have been advocated through the years by vascular surgeons. In this study an everting, running mattress suture of 5-0 silk was used for the majority of the anastomoses. The bleeding from the suture line was slight. The procedure was as easily accomplished as the over-and-over type of anastomosis. It has been said that end-to-end suture technique invariably produces a narrowing of the lumen and that the chance of success in arterial suture is reduced when one is working with a vessel of extremely small size. This was not the case in this study, and when constriction did occur it was only through faulty technique. The type of anastomosis seems not so important as the way in which it is done. Careful placement of stay sutures with minimal tension, adventitial débridement, oiling the suture, keeping the graft moist, and careful placement of the suture line with the proper tension are a few of the small but important details that are necessary for good technique and satisfactory results.

The potential application of autogenous arterial grafts has opened a new frontier for vascular surgeons. The surgical treatment of disease of the coronary arteries, now in its infancy, may possibly advance in the future with the use of such grafts. The size of these vessels need no longer be a deterrent factor. Schlesinger and Zoll[12] found 69 per cent of the occlusions of the main stem of the coronary arteries to be in the proximal 4 cm. of these vessels measured from their ostia. The point of highest incidence in each vessel was not directly at the mouth but 2 to 3 cm. from it. The highest single concentration was in a zone 2 to 3 cm. from the mouth of the left anterior descending branch. Experimental coronary arteriography has been described and is remarkably

accurate in locating sites of narrowing and occlusion in the coronary tree. Many vessels of this size may be sacrificed with impunity from other parts of the body and serve as a steady source of material.

SUMMARY AND CONCLUSIONS

This study of grafts of small arteries has included specimens from 20 mongrel dogs. The grafts were autogenous and had average outside diameters of 3.04 mm. and inside diameters of 1.6 mm. Gross and histologic examinations were carried out 12 to 66 days after the initial procedure. Eighty per cent of the grafts were patent and in all instances remained viable. The histologic appearance of the graft was similar to that of the host artery.

End-to-end anastomosis was used, and suture technique rather than type of anastomosis or size of the vessel appeared to determine future patency. It must be emphasized that the anastomoses were performed by one (N. H. B.) who had had little previous experience with vascular suture technique, and the early results illustrate this clearly.

Small autogenous arterial grafts may prove to be of value in disease of the coronary arteries, in cerebral aneurysm, and in thrombosis of the mesenteric artery. It appears that the size of these vessels is more of a psychologic than a real barrier to their use as grafts in anastomosis of small arteries.

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A SIMPLE DEVICE TO FACILITATE CORONARY ARTERY PERFUSION

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PERFUSION of coronary arteries with oxygenated heparinized blood is a valuable protective measure during cardiac inflow occlusion for cardiotomies performed under hypothermia. Partial oxygenation of the beating but nonworking heart tends to reduce acidosis and hypoxia, thus helping to prevent ventricular fibrillation.

The acomplishment of effective perfusion through the ascending aorta during open heart operations is not difficult but can be cumbersome and unreliable without proper equipment. A simple device is presented which has been employed routinely with uniformly satisfactory results. It is quickly inserted, easily secured, and once in place requires no special attention. Potential damage to the valve cusps or the opposite aortic wall is avoided by the position of the needle point. Leakage around the site of aortic puncture is prevented by the tamponade effect of its fixation.

The instrument consists of a short, 16-gauge hollow needle curved in a small quarter-circle so that it points at 90 degrees from the hub, at a depth not exceeding 7 mm. (Fig. 1). The hub of the needle is welded into a curved metal "saddle" which lies against the aortic wall for stability. A deep groove in this saddle provides a secure seat for a single loose circumferential tie of umbilical tape.

Fresh "arterialized" venous blood is drawn from a donor on the morning of operation after his forearm has been soaked for 20 minutes in water heated to 45° C. The blood is collected in a sterile plastic bag which in turn is connected through a Luer Lok attachment and polyethylene tube to the perfusion needle. The tubing is filled with blood, freed of bubbles, and clamped off before the needle is inserted into the ascending aorta. A single strand of moist umbilical tape is passed around the aorta and is tied in the saddle groove after the needle is inserted into the anterior aortic wall with a curved caudad motion (Fig. 2). Perfusion is started after inflow occulsion begins; the heart is allowed to empty before the pulmonary artery and aorta distal to the needle are cross-clamped.

A perfusion rate of 2 ml. per kilogram of body weight per minute is attempted, but from a practical standpiont the anesthetist merely applies manual compression to the plastic bag, attempting to deliver the unit of blood (500 ml.) during a 5-minute occlusion time. Additional blood is available should the occlusion time exceed this interval.

Although objective data for reliable comparison are not available, clinical evidence suggests that since employing coronary perfusion the myocardial performance has improved. Systemic pressures of more than 100 mm. Hg have been recorded within 30 seconds after restoring the circulation and there has been

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almost instantaneous effective contracture. Before instituting this technique there was often a distressing delay before effective cardiac action was restored. Ventricular fibrillation has not occurred in either group.

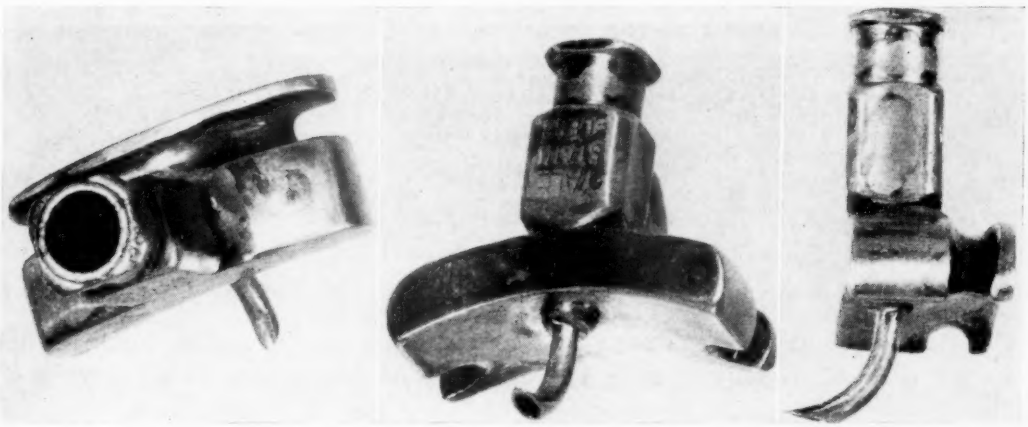

Fig. 1.—Three views of the perfusion needle. Note saddle groove for securing ligature.

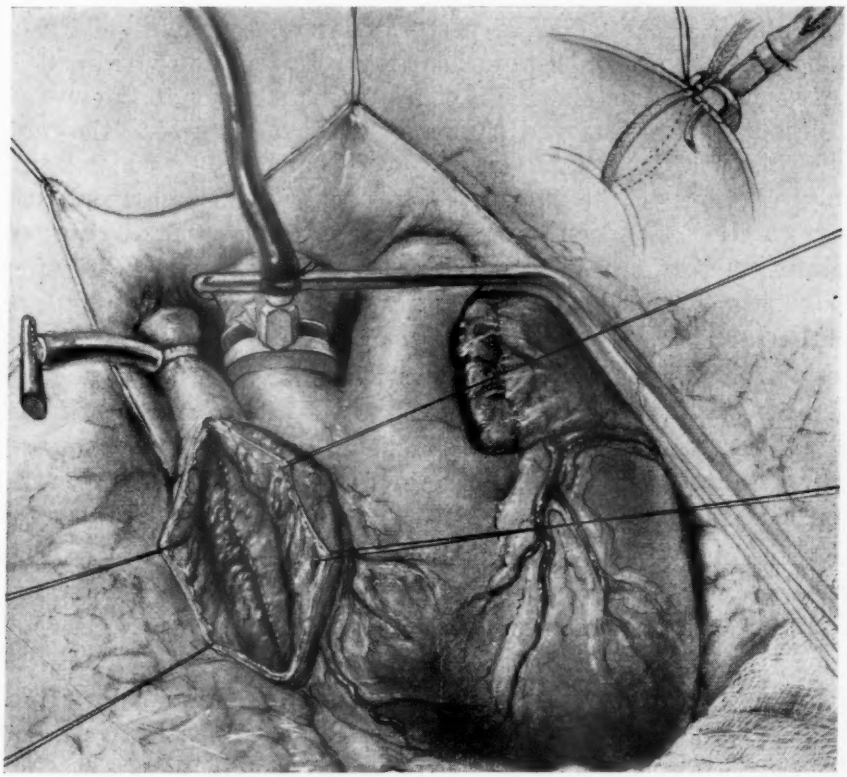

Fig. 2.—Illustration of perfusion needle in place during cardiotomy and caval inflow occlusion. Note clamp occluding great vessels distal to needle. Inset demonstrates position and securing technique.

SUMMARY

A simple device is described which simplifies and facilitates transaortic coronary artery perfusion. Myocardial oxygenation is significantly improved with this procedure during cardiotomy under inflow occlusion.

DRESSINGS: FABRIC VERSUS PLASTIC

A Quantitative Comparison of Fine Mesh Rayon With Perforated Mylar Dressings

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PLASTIC dressings have recently been introduced in increasing numbers for the care of wounds. In general they are of 2 types: a thin, perforated plastic sheet underlying an absorbent pad or a plastic spray applied from an aerosol bomb. Since the latter is not suited to the care of an open running wound, our experience has been with the former. This is characterized by a very thin plastic sheet which is perforated with multiple small holes and covered by a relatively thick absorbent layer to receive the wound exudate. The chief beneficial effect claimed is that of nonadherence to the wound allowing the dressing to be removed painlessly without disturbing the underlying surface. This is a distinct advantage over coarse gauze which can become intimately adherent to the surface of an open wound as a result of the ingrowth of capillaries and epithelium into its interstices making its removal a very painful, bloody, and destructive procedure. There are other important qualities of a good dressing, however, which must be considered. In general, the function of a dressing should be complementary to the natural healing processes. It should provide for the absorption of the wound exudate to avoid surface maceration and for the protection of the wound from mechanical trauma and bacterial infection. It should not interfere with wound healing by exerting a direct toxic or sensitizing effect or by the inhibition of epithelial regeneration.

The principle of the plastic dressing appealed to us at first, but our clinical experience was not encouraging. It was decided to make a comparative study to determine the relative merits of plastic sheet and fine mesh dressings[5] utilizing donor sites from which split-thickness grafts had been taken with a dermatome as in a previous study.[3] Healing under the 2 types of dressings, each covering one-half of the donor site, can be quantitatively compared. Since the depth of the wound and the general systemic factors were identical, differences in epithelization could be attributed to the dressings. Because the purpose of the study was to evaluate the properties of the dressings only, a bactericidal agent was included to minimize the interference of infection with the normal processes of wound healing. The contamination of the dressings

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by the patient's sweat and the incubation of bacteria in the serous exudate can lead to serious infection and maceration of the donor site especially in a hot, humid climate. It was necessary that the bactericidal agent be nonirritating, be nontoxic, have little or no sensitizing effect, be stable in contact with body fluids, be water soluble, and remain effective over a long period of time. For this reason, nitrofurazone (Furacin) in 0.2 per cent solution in a mixture of carbo waxes and polyethylene glycol (Furacin Soluble Dressing) was chosen. Its bactericidal effect against a wide variety of gram-positive and gram-negative organisms was considered a most desirable property. This drug does not interfere with normal wound healing and its property of sensitization has been demonstrated to be much less than previously believed.

METHOD

Fifty unselected donor sites were studied. One half of each was dressed with rayon cloth impregnated with Furacin Soluble Dressing, the other half with a perforated Mylar film backed with fine mesh Furacin-impregnated gauze. The rayon cloth used was a standard material, previously described by Owens. The size of the fiber in this material is 30 denier and the number of threads, warp and weft, 114 by 114, with a thickness of the cloth of 0.0020 mm. The Mylar film was 0.00025 mm. thick with approximately 236 holes per square inch. The holes were 0.6 mm. in diameter and about 1.5 mm. apart. The Mylar plastic sheeting was backed with the Furacin Soluble Dressing-impregnated gauze allowing passage of Furacin through the perforated film to bathe the donor site surface. A similar amount of absorbent coarse mesh gauze was placed over both halves to allow for identical thickness of dressing.

On the third postoperative day each dressing was changed down to the Mylar film or Owens rayon gauze, and an additional layer of Furacin fine mesh gauze was applied, together with a fresh outer dressing of several layers of coarse mesh gauze. All dressings were removed on the fourteenth postoperative day, at which time healing was complete in most cases. Photographs were taken of the donor site at that time, and the halves marked to identify the type of dressing used. These photographic transparencies were then projected onto a thick sheet of cardboard using a standard photographer's enlarging lens and the outlines of the respective areas of donor site were traced. The areas of nonepithelization were carefully cut and weighed on laboratory scales. From the total weight of each donor site and the weight of the nonepithelized portion, the percentage of epithelization was calculated as described in a previous report.[3] Cultures were taken where obvious infection occurred and in representative cases biopsies were made of the different halves of the donor sites. Examples of these photographs are seen in Figs. 1 through 8.

RESULTS

The results of this series are shown in Table I and a comparison with a previous study is made in Table II. Study of Table I reveals 72 per cent

complete healing beneath the Furacin-impregnated rayon as compared with 46 per cent complete healing beneath the perforated Mylar film at the end of 14 days. Ten per cent of the donor sites dressed with Mylar showed no evidence of epithelization. In comparing the 4 types of dressings used, rayon impregnated with Furacin was the most satisfactory and the plastic dressing the least.

TABLE I. DONOR SITE WOUND HEALING IN 50 PATIENTS—EPITHELIZATION OF WOUND HALVES WITH FURACIN-IMPREGNATED RAYON COMPARED WITH MYLAR-BACKED FURACIN-IMPREGNATED FINE MESH GAUZE

NAME	DATE	DAYS POSTOPERATIVE	PER CENT OF EPITHELIZATION	
			RAYON	MYLAR
M. V.	1/18/57	14	100	100
M. A.	1/15/57	14	100	100
W. R.	2/26/57	14	100	100
S. B. II	4/8/57	14	100	100
S. B. I	4/8/57	14	100	100
M. G.	11/14/56	14	100	100
M. T.	11/12/56	14	100	100
S. S.	10/12/56	14	100	100
J. C.	3/4/57	14	100	100
T. S.	2/12/57	14	100	100
M. B.	2/12/57	14	100	100
P. J. II	4/8/57	14	100	100
S. A. I	3/6/57	9	100	100
S. A. II	3/6/57	9	100	100
R. S. II	3/14/57	14	100	100
P. J. I	4/8/57	14	100	100
F. J. T.	11/12/56	14	100	100
Q. J.	11/21/56	14	100	100
E. L. I	11/17/56	14	100	100
E. L. II	11/17/56	14	100	100
M. K.	11/13/56	14	100	100
B. S. A.	10/2/56	14	100	100
M. S.	1/6/57	14	100	100
H. M.	3/14/57	14	100	97
S. A. III	3/6/57	9	100	94
P. E.	12/13/56	14	100	93
P. E. II	1/19/57	14	100	90
P. E. III	12/13/56	14	100	90
S. A. IV	3/6/57	9	100	84
R. S.	3/14/57	14	100	76
A. G.	11/21/57	14	100	50
F. B.	12/20/56	14	100	0
M. G. II	11/14/56	14	100	0
P. E. IV	1/19/57	14	100	0
M. S.	12/13/56	14	100	0
P. E. V	1/19/57	14	100	0
H. M. II	3/14/57	14	98	21
A. G. II	11/21/56	14	98	70
H. M. III	3/14/57	14	98	25
H. M. IV	3/14/57	14	97	50
P. E. VI	12/13/56	14	96	64
L. S.	3/11/57	14	96	47
S. A. V	3/6/57	9	93	90
P. E. VII	1/19/57	14	91	82
H. M. V	3/14/57	14	88	39
T. C.	1/12/57	14	87	40
C. H.	3/9/57	14	88	70
C. H. II	3/9/57	14	84	13
R. S. II	3/14/57	14	80	60
L. S. II	3/11/57	14	57	36

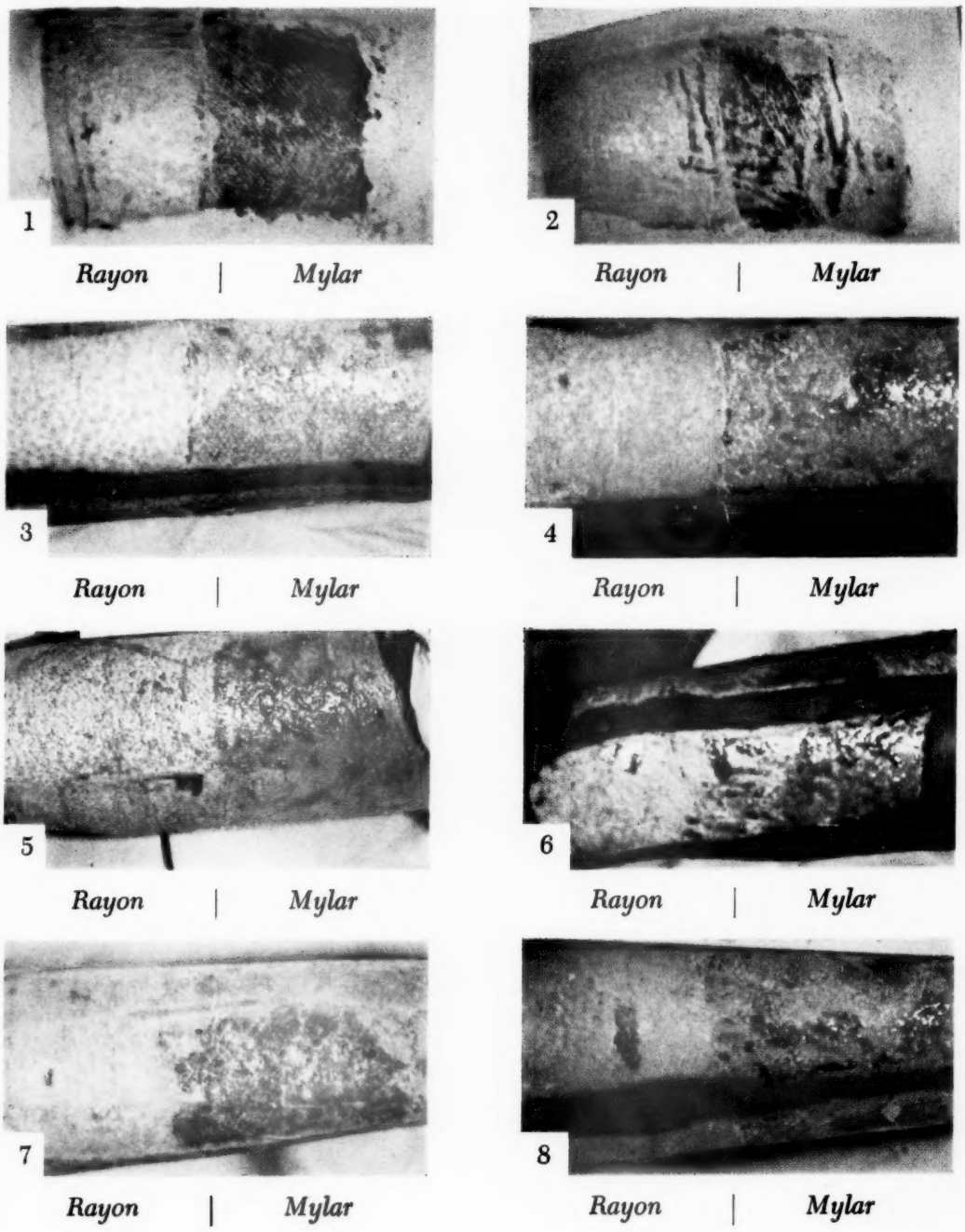

Fig. 1 Illustrations 1 and 2 show the accumulation of blood beneath the Mylar film indicating inadequate drainage. Illustrations 3 to 8 manifest the more complete epithelization of the donor site beneath the FURACIN-impregnated rayon dressing at the end of two weeks.

TABLE II. COMPARISON OF DONOR SITE HEALING WITH VARIOUS DRESSINGS

		FURACIN IMPREGNATED		
	PETROLATUM*	44 MESH GAUZE*	RAYON	MYLAR
Group 1—percentage with 100 per cent epithelization	36	58	72	46
Group 2—percentage with over 75 per cent epithelization	72	78	98	64
Group 3—percentage with under 50 per cent epithelization	16	6	0	24
Group 4—percentage with 0 per cent epithelization	4	4	0	10

*Results of previous study.[3]

CONCLUSIONS

A very fine mesh rayon gauze impregnated with a water-soluble antibacterial agent of long action (Furacin Soluble Dressing) proved to be the most suitable dressing for an open wound in this study. It allows generalized, rather than localized, drainage of the serosanguineous exudate between its interstices but does not admit penetration of capillary or epithelial buds. This generalized drainage appears to be much superior to the localized type provided by perforations of the plastic film. The rayon gauze dressing was removed painlessly when healing was advanced, without adherence or stripping of the thin superficial epithelial surface.

There was no evidence of sensitization or other adverse reaction to the Furacin Soluble Dressing incorporated in the various applications in the 150 halves of donor sites used in this and the previous study. Infection was reduced to a minimum and, when present, was controlled by compresses and frequent dressing changes.

The relatively poor epithelization associated with the plastic dressing may be attributed to maceration related to infection or the excessive accumulation of tissue fluids beneath the plastic film as a result of insufficient drainage. Although the Mylar film did allow escape of tissue fluids, these secretions frequently clotted obstructing the small perforations leading to severe maceration in some cases. Occasional cultures showed a predominance of *Micrococcus pyogenes var. aureus,* as had previously been reported in Liedberg's series,[4] but gross infection was not a prominent feature of the study. Another explanation for the poor epithelization beneath the plastic film could be a direct inhibiting effect on the regenerating epithelium. This has previously been described by Gilman.[1, 2]

SUMMARY

A quantitative comparison of wound healing was carried out in a study of fabric and plastic dressings on 50 donor sites. Very fine mesh rayon gauze impregnated with Furacin Soluble Dressing was found to be superior to all other dressings studied in regard to the extent of epithelization of the underlying wound. Inadequate drainage and the possible direct suppression of regenerating epithelium were believed to be 2 characteristics of the perforated

plastic dressing which reduced its effectiveness. These findings have direct application to the dressing of all open wounds including second and third degree burns.

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A STUDY OF POSSIBLE HUMORAL FACTORS IN LIVER REGENERATION IN THE RAT

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THE vast potential of adult liver tissue for rapid, compensatory hyperplasia in response to partial hepatectomy has been repeatedly demonstrated. Within a few hours, previously resting, mitotically inactive, liver cells begin to undergo mitosis at rates even exceeding the growth rates in embryonic tissue.[11] The repair of nearly all pathologic changes in the liver is effected in some degree by a similar parenchymal regeneration. The biologic *modus operandi* for such a surge of cellular growth and proliferation has never been fully explained. Indirect evidence suggests that a humoral factor appears in the host in response to hepatectomy which is capable of inducing and potentiating growth of liver tissue. The aim of this study was to directly demonstrate the presence of such a growth factor and to study the effect of this factor upon normal liver tissue in vivo.

Following a standard partial hepatectomy in rats or in dogs, restoration of the resected liver tissue follows a constant, predictable course. After a latent period during the first 12 hours, the residual liver rapidly hypertrophies, increasing in weight by 50 per cent at the end of 24 hours.[15] The appearance of active mitosis is more delayed but reaches an average rate of 21.3 mitoses per 1,000 cells at the end of 24 hours[5]; the maximum mitotic rate in normal resting liver tissue is 0.1 mitosis per 1,000 cells. The peak increment in weight occurs during the third day following hepatectomy.[4]

Glinos and Gey[12] found that serum obtained from recently hepatectomized rats stimulated the growth of tissue cultures, whereas serum from sham operated animals had no such effect. They also observed evidence of cellular hyperplasia in the livers of rats in which the concentration of the plasma proteins was decreased in vivo by plasmophoresis. From their studies, they postulated the presence of a growth inhibiting factor in normal plasma which is decreased during the regenerative phase following hepatectomy. Several studies using parabiotic rat preparations have demonstrated evidence of cellular proliferation in the liver of one parabion following partial hepatectomy in the other parabion.[1, 7, 9, 25] Bucher and co-workers[7] found even greater evidence of hyperplasia in the liver of the unoperated middle member of parabiotic triplet preparations in response to the greater stimulus caused by simultaneous 80 per cent partial hepatectomies in the other 2 members of the trio.

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PLAN OF THE STUDY

The effect of repeated intravenous infusions of normal rat plasma or of plasma collected from recently hepatectomized donor rats was studied upon cellular growth in the rat liver in vivo. The effects of such plasma infusions were observed first in relation to the expected regenerative response in the livers of rats recently hepatectomized; second, they were observed in relation to evidences of cellular proliferation in nonoperated rats with normal resting livers.

In order to study cellular growth and proliferation, the following indices were measured: (1) changes in liver weight; (2) the amount of incorporation of a tracer isotope, P^{32}, into liver desoxyribonucleic acid (DNA), reported in the literature as an index of the rate of cell divisions; and (3) the incidence of mitosis among the parenchymal cell nuclei of the liver.

METHODS AND MATERIALS

Female albino rats of a uniform strain,* weighing 145 to 245 Gm., were used. Some of the rats studied underwent partial hepatectomies according to the method of Higgins and Anderson.[15] In a control series, it was found that an average 67.1 per cent of the total liver was removed by this procedure. Since all experiments were of short duration, no special emphasis was placed on aseptic technique. Excluding mortalities due to technical error at operation, no postoperative mortalities occurred in the groups reported. None of the animals were fasted, either prior to surgery or following hepatectomy, and no supplemental carbohydrate was offered in the drinking water, as has been done in some studies. Animals were fed *ad libitum* with stock laboratory rat pellets.

All hepatectomies in the experimental rats were performed and all animals sacrificed between 8 A.M. and 10 A.M., so that consistent allowance was made for the normal diurnal variation in mitotic activity demonstrated by Jaffee.[16]

Each animal was given a tracer dose of 0.2 μc of P^{32} per gram of body weight by intraperitoneal injection 20 hours after partial hepatectomy or 20 hours after the first plasma infusion in the case of the nonoperated animals.

All experimental groups were sacrificed by exsanguination 48 hours following hepatectomy or following the first plasma infusion in the nonoperated groups. The liver was removed from each animal as quickly as possible, drained free of blood, and weighed. A portion of the caudate lobe was fixed in Bouin's solution for histologic sections and the remainder of the liver was frozen for later DNA extraction.

Routine hematoxylin and eosin stained histologic sections were prepared for mitotic counts. Only parenchymal nuclei were counted using the techniques outlined by Brues and Marble[5] and by Bucher and associates.[7] A minimum of 1,000 nuclei were counted and more than 2,000 counted when less than 20 mitoses were observed per 1,000 nuclei.

Suitable samples of the frozen liver were homogenized, and DNA was extracted using a modification of the perchloric acid hydrolysis method of Ogur and Rosen.[21] The concentration of the DNA hydrolysate was measured in a

*Obtained from the Holtzman Rat Co., Madison, Wis.

Beckman quartz spectrophotometer at 260 mμ. The radioactivity in 1 ml. of the DNA hydrolysate was measured as counts per minute (cpm) by a Tracerlab Precision Ratemeter. The results have been reported as the specific activity of the DNA fraction. In order to give values comparable to others previously reported, the figures have been converted to counts per minute per DNA-phosphorus. DNA-phosphorus was calculated from DNA by multiplying by a factor of 0.099.[23]

Plasma for intravenous injection into the experimental animals was obtained by exsanguination of donor animals under ether anesthesia, collecting the blood from the occluded abdominal aorta using sodium citrate as an anticoagulant. The donor blood was pooled, centrifuged, and the supernatant plasma immediately infused into either a tail vein or a hindleg vein of the experimental animals. When posthepatectomy plasma was needed, the donor animals underwent the standard partial hepatectomy 24 hours prior to the time the plasma was collected.

OUTLINE OF THE EXPERIMENT

Group 1 (5 rats).—These animals served as hepatectomy controls and received no treatment following operation except injection of the tracer isotope.

Group 2 (5 rats).—Following the standard hepatectomy, 1 ml. of plasma, freshly obtained from normal donor rats, was administered intravenously every 8 hours (5 doses) until the animals were sacrificed after 48 hours.

Group 3 (5 rats).—Following the standard hepatectomy, these rats were treated according to the schedule outlined in the preceding paragraph for Group 2, except that the plasma used for infusion was collected from donor rats hepatectomized 24 hours prior to collection.

Group 4 (4 rats).—These animals, serving as nonoperated controls, received no treatment except for the intraperitoneal injection of the tracer isotope.

Group 5 (5 rats).—Nonoperated normal rats were given 1 ml. intravenous injections of normal rat plasma every 8 hours (6 doses) and were sacrificed after 48 hours of such infusions.

Group 6 (5 rats).—Nonoperated normal rats were treated as outlined for Group 5 in the preceding paragraph except that the plasma used was collected from recently hepatectomized donors.

The details of the management of each group have been outlined in Fig. 1.

RESULTS AND DISCUSSION

The period of 48 hours for treatment of the experimental animals was chosen so that the animals would be sacrificed at a time when the most active growth and cellular division might be expected on the basis of previous observations of normal regeneration following partial hepatectomy.[4, 15] A similar period was found to be associated with the greatest increase in cellular proliferation in the parabiotic rat experiments previously noted.[7, 9, 25] It was assumed that a humoral factor mediating this growth ought to reach maximal concentration

earlier; therefore, the posthepatectomy plasma was collected 24 hours following partial hepatectomy in the donor animals. Previous studies in the rat of plasma protein fractions and of plasma volume in response to hepatectomy have demonstrated significant falls in both during the first 24 hours after operation.[8, 18]

The 1 ml. volume of plasma chosen for intravenous infusion represents a considerable transfusion in animals of this size. The rat's normal blood volume is reported to be approximately 0.06 ml. per gram of body weight,[10] or roughly 12 ml. for a 200 Gm. animal; therefore, it is estimated that a volume of plasma equivalent to nearly 15 per cent of the animal's total plasma volume was administered with each infusion, or a total volume equal to three-fourths of the animal's total plasma volume during the course of the experiment.

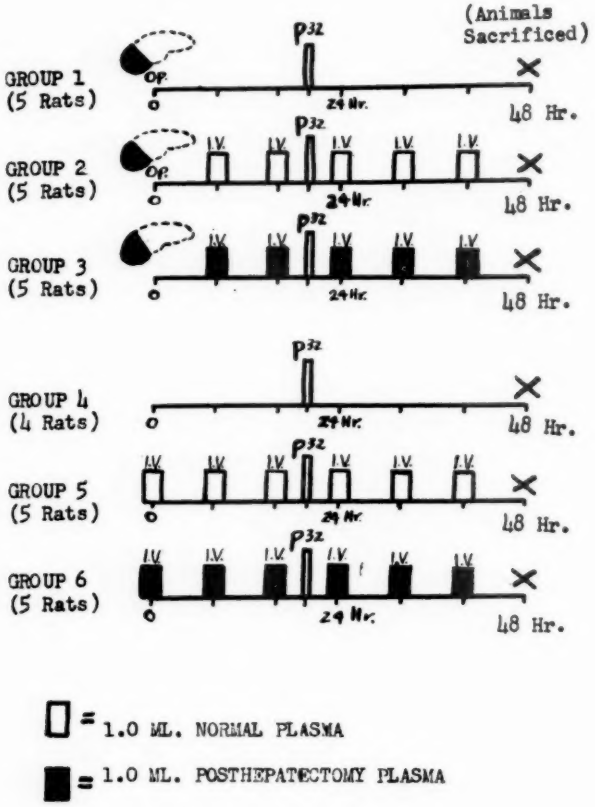

Fig. 1.—Outline of experiment.

Changes in liver mass, in specific activity of DNA-phosphorus, and in mitotic activity rate will be reported for each experimental group.

Change in liver weight following hepatectomy as a measure of regeneration has been expressed in many ways in the literature. The most understandable would appear to be the percentage of replacement of the resected portion of the liver at any given time following hepatectomy. There has thus been 50 per cent regeneration when the remaining liver tissue has increased until one-half of the removed tissue has been replaced. In the nonoperated rats, the percentage of regeneration by weight is not applicable. Instead, the final liver weight

was compared to the weight predicted in relation to the rat's body weight as was done by Higgins and Anderson[15]; they found a standard deviation of ±3 per cent in the mean liver weight in their control series.

Using tracer isotopes, the dynamics of DNA metabolism in the rat liver have been extensively studied. In resting liver tissue, DNA is biochemically inert.[2, 3, 13, 24] During the initial phase of regeneration, the DNA concentration in whole liver tissue remains essentially unchanged, although the concentration of DNA in the average cell nucleus has been found to increase nearly twofold between 12 and 24 hours following hepatectomy,[22] returning to normal concentrations thereafter. There is a rapid incorporation of P^{32} into the newly-formed DNA in proliferating liver tissue.[6, 17, 19] Once formed, the new DNA is again biochemically stable[14, 20] even during subsequent cell divisions.[3] Therefore, Nygaard and Rusch[20] have concluded that in liver tissue "DNA synthesis can serve as an indicator of cell division, and, consequently, measurements of P^{32} incorporation into DNA may be used in the study of factors influencing the rate of mitosis."

Brues and Marble[5] established that mitoses occur uniformly throughout the liver parenchyma at any given time but that there is a considerable variation in the counts observed in individual animals at equal periods after hepatectomy. They observed counts ranging from 0.0 to 44.0 per 10^3 cells at 48 hours after partial hepatectomy. This normal spread in the counts observed in any series limits the value of this measure of regeneration. In addition, the method is tedious and open to subjective uncertainties in choosing the mitotic figures. Despite these criticisms, such counts were done because this measure has been the basis for conclusion in many of the studies cited.[1, 7, 9, 12, 25]

Hepatectomy Groups (Table I).—Hepatectomized controls (Group 1): The average percentage of regeneration observed was 47 per cent. This compares favorably with that observed by other authors 48 hours after similar partial hepatectomies in rats.[4, 15] The average specific activity of DNA-phosphorus was 26.7 cpm/μg DNAP. The average mitotic activity was 22.9 mitoses per 10^3 cells. This result is higher than the mean count of 9.7 mitoses per 10^3 cells reported by Brues and Marble[5] at the same period after hepatectomy, but all of the individual counts recorded were well within the range of 0.0 to 44.0 mitoses per 10^3 reported by these authors.

The effect of normal plasma upon the expected liver regeneration 48 hours following partial hepatectomy (Group 2): The average percentage of regeneration by weight (31 per cent) and the average specific activity of DNA-phosphorus (8.4 cpm/μg DNAP) both indicate that normal regeneration was impeded by the injections of normal plasma. This would support the hypothesis of Glinos and Gey[12] that the humoral effect of hepatectomy is to decrease a restraining factor normally present in plasma. The average mitotic activity in this group (31.0 mitoses per 10^3 cells) was greater than the average control value, although there is considerable overlap of the individual counts in the 2 groups. This suggests that the DNA specific activity does not directly reflect actual mitosis of cells and that there may be a dissociation between nuclear

biochemical activity and actual cell division, a dissociation that will be observed in another group in this study. Normal plasma impeded growth in weight and in newly-formed DNA but did not impede cell division.

The effect of posthepatectomy plasma infusions upon liver regeneration following partial hepatectomy (Group 3): There was no significant increase in the average weight regeneration (50 per cent) when compared with the control group (47 per cent). There is considerable overlap in the individual results in the 2 groups. However, the incorporation of P^{32} into new DNA was increased (33.5 cpm/μg DNAP) as was the average mitotic activity (39.2 mitoses per 10^3 cells) when these results are compared to the control means. In addition, there is no overlap of the individual results when the lowest of these is compared with the highest of the individual control figures. It is apparent that posthepatectomy plasma augmented normal regeneration, except in terms of weight increase. It is probable that a larger experimental stimulus (either a continuous infusion or larger individual infusions of posthepatectomy plasma) would have caused a significant augmentation in weight gain as well.

TABLE I. RESULTS OF PLASMA INFUSIONS IN HEPATECTOMIZED RATS

RAT NUMBER	PER CENT REGENERATION (BY WEIGHT)	DNA-PHOSPHORUS SPECIFIC ACTIVITY (CPM/μG DNAP)	MITOTIC ACTIVITY (MITOSES PER 10^3 CELLS)
	Group 1. Hepatectomized Controls		
1	31	26.8	26.6
2	40	25.5	16.8
3	71	28.3	19.8
4	55	21.6	31.7
5	37	31.4	19.4
Average	47	26.7	22.9
	Group 2. Hepatectomy, Normal Plasma		
1	33	7.7	12.3
2	29	6.2	33.5
3	28	15.5	35.9
4	39	5.1	47.6
5	27	7.5	25.9
Average	31	8.4	31.0
	Group 3. Hepatectomy, Posthepatectomy Plasma		
1	43	34.1	37.6
2	43	34.2	43.0
3	34	32.5	36.0
4	84	34.1	45.6
5	48	32.8	34.0
Average	50	33.5	39.2

Nonoperated Groups (Table II).—Normal controls (Group 4): Only specific activity of DNA-phosphorus and the mitotic activity of resting liver was determined. The averages were 4.9 cpm/μg DNAP and 0.19 mitosis per 10^3 cells. Both figures indicate only minimal cellular growth activity when compared to the figures for actively regenerating liver tissue observed in Group 1.

The effect of normal plasma infusions in nonoperated rats (Group 5): The final liver weight was compared with the liver weight predicted on the basis of the animal's body weight at the time of sacrifice. The average increase in liver weight of 3 per cent was not a significant change. The average specific activity

of DNA-phosphorus in this group was 0.9 cpm/μg DNAP. However, in this same group, the average mitotic activity was 1.4 mitoses per 10^3 cells, which is a small but definite increase of nearly eightfold in comparison with the average control value in Group 4. The dissociation of the mitotic activity from the DNA activity is again observed, as was noted in Group 2. In both groups, there is an absence of increased incorporation of P^{32} into DNA at a time when there is increased mitotic activity. Apparently changes in mitotic activity are not always associated with comparable changes in the formation of new DNA.

The effects of posthepatectomy plasma infusions in nonoperated rats (Group 6): The average increase in predicted weight of the liver in this group was 4 per cent; this is a barely significant increase from the normal in view of the previously reported standard deviation. The average specific activity of DNA-phosphorus in this group was the highest observed in any of the experimental groups (39.6 cpm/μg DNAP). Since the average mitotic activity in this group was only 2.0 mitoses per 10^3 cells, the evidence that posthepatectomy plasma will induce cellular proliferation in resting liver tissue is much less striking than the evidence for increased nuclear growth. It has been observed that there is a steady increase in the amount of DNA per nucleus from 12 hours after partial hepatectomy up to the time when there is a detectable increase in frequency of mitosis[22] and that during this same period before the appearance of increased mitotic activity, there is a rapid increase in incorporation of P^{32} into the newly synthesized DNA.[20] Thus it is possible that the observed high specific activity in Group 6 without a concomitant increase in mitotic activity reflects this latent period of rapid incorporation of P^{32} prior to the appearance of mitotic activity. Certainly the results in Group 6 indicate that posthepatectomy plasma is capable of inducing increased cellular growth activity and is probably responsible for inducing cellular proliferation.

TABLE II. RESULTS OF PLASMA INFUSIONS IN NONOPERATED RATS

RAT NUMBER	PER CENT CHANGE IN PREDICTED LIVER WEIGHT	DNA-PHOSPHORUS SPECIFIC ACTIVITY (CPM/μG DNAP)	MITOTIC ACTIVITY (MITOSES PER 10^3 CELLS)
	Group 4. Normal Controls		
1	—	4.7	0.35
2	—	3.7	0.09
3	—	5.4	0.30
4	—	5.6	0.00
Average		4.9	0.19
	Group 5. Nonoperated, Normal Plasma		
1	0	0.8	1.10
2	−6	0.9	0.90
3	+10	0.8	2.90
4	−2	0.9	0.50
5	+12	0.9	1.60
Average	+3	0.9	1.40
	Group 6. Nonoperated, Posthepatectomy Plasma		
1	+5	40.7	0.60
2	+5	41.3	0.60
3	+8	42.8	4.60
4	−5	36.0	1.30
5	+6	37.4	2.70
Average	+4	39.6	2.00

SUMMARY

1. The results of this study indicate that a humoral change capable of influencing cellular hyperplasia does occur in response to hepatectomy in the rat.

2. When plasma collected from recently hepatectomized rats is infused intravenously into other rats similarly hepatectomized, there is an increase in the expected growth and cellular proliferation in the residual liver. When post-hepatectomy plasma is infused into nonoperated rats, there is evidence of cell growth and mitotic activity in the liver.

3. When plasma collected from normal rats is infused intravenously into recently hepatectomized rats, there is a decrease in the expected growth in weight and in the expected rapid incorporation of P^{32} into DNA, although cellular mitotic activity is undiminished.

4. In 2 groups receiving normal plasma, a dissociation of DNA-phosphorus specific activity and mitotic activity was observed. Very little incorporation of P^{32} into DNA occurred despite the presence of increased mitotic activity.

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UROKON PORTOGRAMS IN DOGS

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THE introduction of x-ray contrast media into the portal circulation has been extremely useful in the diagnosis and investigation of portal hypertension.[1, 5, 6] While there has developed a large literature on the intravascular use of Urokon, we have been unable to find studies on the effect of the dye upon the liver when injected directly into the portal system.[2-4, 9] Correspondence with the manufacturer lends credence to this view.[7] A clinical case of acute hepatic failure following a portogram and a portacaval anastomosis prompted this brief study.

Thirteen adult mongrel dogs were used. Bromsulphalein tests were done initially, at 3 days after the injection, and at 10 days after the injection. A spectrophotometric adaptation of the method of Rosenthal and White[8] was used by our biochemistry laboratory for these determinations. A Bromsulphalein dosage of 5 mg. per kilogram of body weight was used. After the initial Bromsulphalein tests, the animals were lightly anesthetized with sodium pentobarbital and the abdomen opened. A generous liver biopsy was taken and a needle placed in a large branch of the superior mesenteric vein just distal to the portal vein. A 2.2 c.c. dose of 70 per cent Urokon per kilogram of body weight was injected through this needle into the p[illegible]stem (this is about 5 times the amount we use in the human cases). [illegible]bdomen was closed and the animals were maintained on standard kennel rations with no drug therapy. On the tenth postoperative day, after the third Bromsulphalein test, the dogs were reanesthetized and the abdomen reopened. Another liver biopsy was then performed.

TABLE I. BROMSULPHALEIN DETERMINATIONS

DOG NUMBER	PREOPERATIVE (PER CENT)		3 DAYS POSTOPERATIVE (PER CENT)		10 DAYS POSTOPERATIVE (PER CENT)	
	15 MIN.	30 MIN.	15 MIN.	30 MIN.	15 MIN.	30 MIN.
1	3.5	3.5	4.0	1.8	2.5	1.8
2	6.5	2.0	1.5	0.0	1.5	0.0
3	4.5	0.0	1.5	0.0	1.5	0.0
4	5.0	1.0	2.4	0.0	2.5	0.0
5	1.5	1.5	3.7	2.0	3.5	1.5
6	2.5	1.8	3.7	2.0	3.5	1.5
7	1.5	0.0	1.7	0.0	5.0	1.5
8	2.7	2.2	5.5	2.7	5.5	1.9
9	6.8	2.2	3.7	0.0	10.5	3.0
10	8.5	5.0	1.8	0.0	7.0	1.5
11	20.0	11.0	10.8	6.8	11.5	6.0
12	12.5	5.5	1.5	0.0	5.4	3.0
13	22.0	18.0	10.0	6.4	19.0	13.5

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Table I shows the results of the Bromsulphalein tests. Three of the 13 animals had abnormal Bromsulphalein excretion before the dye was injected. In these, as well as in the remainder of the dogs, no marked change in the Bromsulphalein excretion was found at 3 and 10 days after surgery.

The liver biopsies before and after the portal injection were examined by me and by 3 pathologists. No abnormality of the liver histology before or after the Urokon injection was found.

SUMMARY

Injection of 1 c.c. per pound of body weight of 70 per cent Urokon directly into the portal venous system had *no* significant effect upon the liver as measured by Bromsulphalein excretions and microscopic examination in this study.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

BECAUSE of the increasing importance of Pediatric Surgery, the Editorial Board of SURGERY, after considerable deliberation, decided to establish a Section devoted to this specialty of medicine. We are fortunate to have Dr. Mark M. Ravitch edit the Section, and it is anticipated that it will be a real contribution to medicine. The Section appears for the first time in the present issue of SURGERY.

—The Editors

TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

REPORT OF A CASE WITH COMPLETE SURGICAL CORRECTION

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THE first operation for total anomalous pulmonary venous connection was performed in 1950 without success.[5] Subsequently, partial revision of the abnormality was accomplished in 9 cases, using an extracardiac approach.[6, 8-10] Following the development of intracardiac techniques, Lewis[6] performed the first successful complete correction of this anomaly. Eleven successful complete repairs have now been accomplished.[3, 4, 7] It is the purpose of this communication to report an additional case.

ANATOMIC CONSIDERATIONS

With connection of all the pulmonary veins to the systemic venous system, all of the blood must return to the right atrium. The only route by which blood can enter the left atrium is by way of an interatrial orifice, and either a patent foramen ovale or an atrial septal defect is present in all cases of this malformation.

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In total anomalous pulmonary venous connection, the pulmonary veins from both lungs usually converge to form a common venous trunk which then joins the systemic venous return at a single point. In review of 113 cases of this anomaly without associated major cardiac malformations, only 8 exceptions were found to this pattern.[2] The common site of connection is to the left innominate vein. The right atrium, coronary sinus, and superior vena cava are the next most frequent sites of connection, in that order. Less often, the connection may be to the inferior vena cava or into the portal system below the diaphragm.

When the anomalous venous connection is to the right atrium, there is a chamberlike recess in the posterior aspect of the right atrium into which empty the pulmonary veins in close proximity to one another. When the pulmonary veins connect elsewhere to the systemic venous circulation, they ordinarily form a sinus in the mediastinum posterior to the heart. A single trunk emerges from this sinus to form the final junction with the systemic venous return. This anatomic pattern has particular surgical significance which will be discussed below.

PATHOPHYSIOLOGY

Since all pulmonary venous return enters the right side of the heart, there is a mixing of unsaturated systemic blood and saturated pulmonary venous blood. From this common mixed venous pool, the blood divides into 2 pathways. A major portion of the blood is recirculated through the pulmonary bed; this represents an abnormally high flow in the lesser circulation. The alternative pathway of flow is across the atrial septal defect into the systemic circulation.

Two mechanisms for development of abnormal resistance are present within the right side of the heart. First, the increased flow through the pulmonary bed may cause a progressively increasing pulmonary vascular resistance. As pointed out by Burchell,[1] the pulmonary flow will then decrease, and the percentage of oxygenated blood in the mixed venous pool will decrease. As the pressure in the right side rises, cyanosis and heart failure ensue. Second, the small size of the atrial defect may produce resistance to egress of blood from the right atrium into the left atrium. The resistance to flow will increase pressure in the right side of the circulation, causing heart failure to develop.

Eighty per cent of these patients die in heart failure before the age of one year. Those who survive show a clinical course similar to uncomplicated atrial septal defect with little evidence of difficulty from the large pulmonary recirculation until pulmonary hypertension and heart failure develop. By the time symptoms occur, there is serious derangement of cardiac function. Operation may be contraindicated in these cases because of the irreversibility of the pulmonary vascular changes. In the asymptomatic patient, immediate operation is indicated to prevent the development of increasing pulmonary vascular resistance, pulmonary hypertension, and right heart failure.

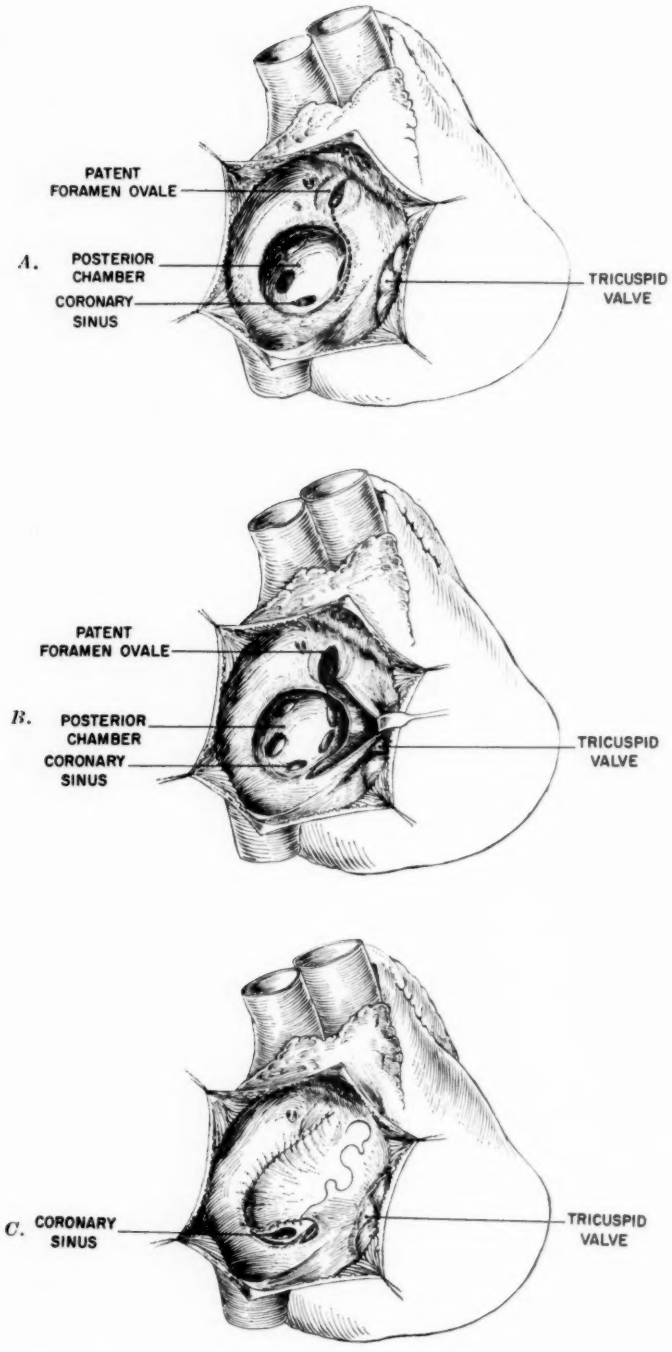

Fig. 1.—*A*, Four pulmonary veins and the coronary sinus are seen to enter a chamberlike recess in the posterior wall of the right atrium. *B*, The interatrial communication has been enlarged by splitting the atrial septum overlying the site of anomalous pulmonary venous connection. *C*, Correction of the malformation has been completed by transposing the atrial septum to the right of the anomalous pulmonary venous entry. The ostium of the coronary sinus has been excluded from the rest of the transposed chamber so that it continues to connect normally to the right atrium.

CASE REPORT

P. K., a 5-year-old white girl, was first seen at this clinic on April 4, 1957. Four weeks prior to this visit the patient had been examined because of a fever and headache. At that time a heart murmur was found for the first time. The patient's mother had noted "bounding" of the patient's left anterior chest since the age of 2 years. There was no history of exercise intolerance, cyanosis, frequent respiratory infections, or heart failure.

Physical Examination.—The patient was a well-developed, slender, white female. A plot of her height and weight on a Wetzel grid indicated that her physical development fell within the eighty-second percentile. Pulse was 120, respiratory rate 20, and blood pressure 105/80. The heart was increased in size with the point of maximal impulse in the fifth left intercostal space at the anterior axillary line. There was prominence of the left anterior chest wall. A grade IV, harsh systolic murmur was maximal in the fifth left intercostal space. The pulmonary second sound was accentuated and split. The liver was palpable 2 fingerbreadths below the right costal margin. No other positive physical findings were present.

Laboratory Findings.—The hemoglobin was 14.7 Gm. per cent and the white blood count was 12,200. Differential count showed an 11 per cent eosinophilia. The electrocardiograms demonstrated mild right ventricular hypertrophy. Chest roentgenograms revealed an increase in the size of the right ventricle and pulmonary outflow tract. Pulmonary vascular shadows were prominent. Results of cardiac catheterization are presented in Table I. An angiocardiogram was interpreted as showing a ventricular septal defect, or possibly an atrial septal defect. The preoperative diagnosis was ventricular septal defect, possible ventricular and atrial defects, or possible atrioventricularis communis.

TABLE I. CARDIAC CATHETERIZATION

LOCATION	PRESSURE	SATURATION (PER CENT)
PA	29/17	92
RV	33/7	92
RA (high)	7/5	72
RA (mid)	11/8	81
RA (low)	11/8	71
IVC	11/7	78
SVC	11/7	63
LPV	19/13	94
LA	13/9	94
BA	98/80	95

Operation.—The patient was operated upon Nov. 7, 1957, using extracorporeal circulation. A modification of the Gibbon pump-oxygenator was employed. Examination of the heart revealed enlargement of the right atrium and right ventricle. After digital exploration of the right atrium had demonstrated the presence of an atrial septal defect, the patient was placed on extracorporeal circulation and a right atriotomy was performed. A large posterior chamber was seen to enter the right atrium just cephalad to the tricuspid valve. The orifice of the coronary sinus was within the chamber close to its inferior margin (Fig. 1, *A*). All of the pulmonary veins emptied anomalously into the right atrium by way of this chamber. The repair was accomplished by enlarging the atrial septal defect found in the fossa ovalis (Fig. 1, *B*) and transposing the atrial septum to the right of the chamber. It was technically possible to carry out this repair in such a manner that the coronary sinus drained normally into the right side of the heart. Complete correction of the abnormal circulation was thus accomplished (Fig. 1, *C*).

The patient recovered without complications except for the presence of a first degree heart block, which was still present at the time of discharge 2 weeks postoperatively.

DISCUSSION

Among the 46 operated cases of total anomalous pulmonary venous connection which we have been able to tabulate, 12 have been completely corrected. The first patient, operated upon by Lewis,[6] was repaired under hypothermia; in the second patient, the atrial well technique was used by Kirklin[3] to correct the anomaly. The remaining 10 patients were repaired utilizing extracorporeal circulation. The total number of cases reported in which extracorporeal circulation has been used is 15; thus, completely successful correction has been achieved in 66 per cent of these cases.

Attempts at partial correction of the malformation have been made in 29 instances.* The approach has been an extracardiac one, with an attempt to anastomose the pulmonary venous return to the left atrium. No attempt was made to repair the atrial septal defect in any of these cases. Only 9 of these patients have survived (31 per cent), and there exists the necessity for further surgery in all of them. This 2-stage approach has been recommended because of the diminutive size of the left side of the heart ordinarily found in these cases.[10] It was postulated that complete correction of the anomaly would result in acute left heart failure.

The successful surgical corrections of total anomalous pulmonary venous connection have been made in those instances in which the connection was to the right atrium, the left innominate vein, or the coronary sinus. It is noteworthy that total anomalous pulmonary venous connections of these general anatomic types comprise 78.9 per cent of all cases of the anomaly without associated major cardiac malformations.[2] Thus, operative techniques are presently available by which the majority of these malformations can be completely corrected.

SUMMARY

A case of complete correction of total anomalous pulmonary venous connection is reported. Added to 11 previous cases, this makes a total of 12 instances in which malformation was completely corrected. The anatomy and pathophysiology of this condition are discussed. The merits of various surgical approaches to the problem are evaluated with the conclusion that a one-stage complete repair using extracorporeal circulation is indicated.

ADDENDUM TO CASE REPORT

Following discharge from the hospital, the child continued to improve. She was last seen on June 13, 1958, by Dr. Arthur Moss. At that time she weighed 33 pounds and was 41 inches in height; body temperature was 98.4° F., pulse rate was 68, and blood pressure was 105/74. A grade II systolic murmur was heard along the left sternal margin. The lungs were clear to percussion and auscultation and the incision was well healed. There was no peripheral edema or cyanosis. The child's appetite was good and, according to the mother, her exercise tolerance seemed normal. The electrocardiogram demonstrated a persistent 2-1 heart block. On x-ray examination there was evidence of a decrease in the size of the heart outline.

*References will be supplied by the authors upon request.

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IMPERFORATE ANUS

Report of 130 Cases

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INTRODUCTION

IMPERFORATE anus is a broad term applied to various obstructive malformations of the terminal bowel often associated with anomalies of the genitourinary tract. Inadequate initial treatment gives very poor results. Recent advances in treatment of these anomalies have greatly improved the results and lessened morbidity and mortality considerably. The incidence of imperforate anus to newborn infants has been found to range from 1 per 1,500 to 1 per 25,000. It is generally accepted as approximately 1 per 5,000.

HISTORY

Paulus of Aegina described a successful operation for this anomaly in the seventh century. In 1640, Scultet successfully dilated a case of congenital anal stenosis with gentian roots. Bell of England performed the first perineal dissection in 1787. Amussat, in 1835, recommended proctoplasty by careful dissection of the perineum, mobilization of the rectum, and suture of the rectum to the anal site. The first successful operation for this anomaly in this country was done by Campbell in 1790. Many other reports have followed (Crowell[6] and Brenner[3]).

EMBRYOLOGY

In the 5-week embryo, the cloaca is a terminal cavity common to the urogenital sinus and posterior intestinal tract. The cloacal membrane, separating the cloaca from the exterior, is divided into the anal membrane and urogenital membrane by the seventh week. The cloaca is divided into the urogenital sinus and the intestine in two ways. The urorectal septum, composed of mesenchyme, descends between the 2 and at the same time there is ingrowth of the mesenchyme of the lateral walls toward the midline. Failure of fusion of these septa results in fistulas. By the seventh week the 2 cavities are usually separated and communicate with the exterior by rupture of the urogenital and anal membrane. The proctodeum is formed by invagination at the anal pit. Continuity with the rectum is established by rupture of the anal membrane. The anal sphincters develop independently from the regional mesenchyme. In the female, the Müllerian ducts are attached to the posterior urogenital sinus and, as they descend, take over any fistula between the rectum and urogenital sinus.

Received for publication Nov. 14, 1957.

CLASSIFICATION

The following classification by Ladd and Gross[15] is used: Type I, incomplete rupture of the anal membrane or stenosis at a point 1 to 4 cm. above the anus; Type II, imperforate anus due to persistent membrane; Type III, imperforate anus but with rectal pouch separated from the anal membrane and terminating blindly either within or above the pelvis; and Type IV, normal anus with rectal pouch ending blindly. The anal and rectal pouches sometimes are separated only by a membrane. The 4 types are demonstrated in Fig. 1.

A fistula may occur with any type but is much more common with Type III. The 3 types of fistula occurring in males are rectourethral, rectovesical, and rectoperineal. In the female, rectoperineal, rectovaginal, and rectovesical occur, although the last named is a very rare finding.

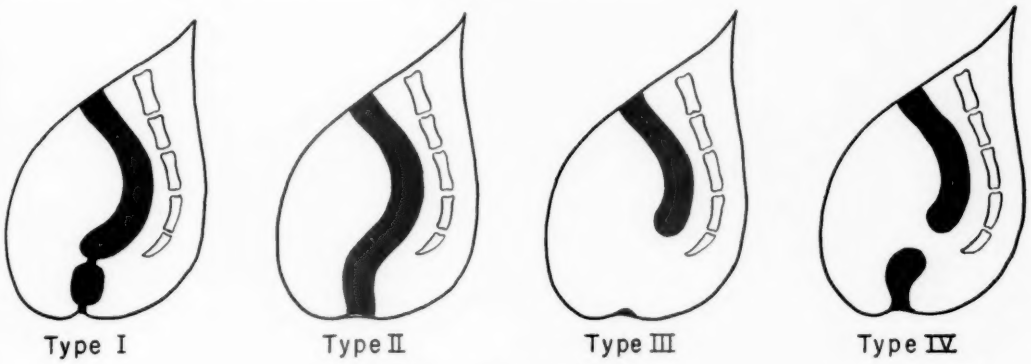

Fig. 1.—Types of imperforate anus.

REPORT OF SERIES

At the University of Michigan Hospital 130 cases were seen from 1931 to the middle of 1955. Distribution as to sex and type is given in Table I.

TABLE I

TYPES	MALE	FEMALE	TOTAL
I	0	0	0
II	9	14	23
III	49	58	107
IV	0	0	0
Totals	58	72	130

FISTULAS

Eighty-three patients (64 per cent) in this group had an associated fistula. One female patient had a rectovesical and a rectovaginal fistula making the total number of fistulas 84. One other is listed here as a rectovesical fistula in a female, but the urologist believed this child to be a male. The sex was never definitely determined. Nine of the 23 patients having Type II anomaly had a fistula, and 74 with the Type III anomaly had a fistula. Distribution of fistulas as to sex is given in Table II.

TABLE II

TYPE OF FISTULA	MALE	FEMALE	TOTAL
Rectoperineal	9	23	32
Rectovaginal	0	32	32
Rectovesical	9	2*	11
Rectourethral	9	0	9
Totals	27	57	84

*One was female with both rectovaginal and rectovesical fistula. One was a patient the urologists believed to be a male.

ASSOCIATED ANOMALIES

Many infants born with imperforate anus have other congenital anomalies and these add perceptibly to the morbidity and mortality. Sixty-two of the 130 patients (48 per cent) had at least one other anomaly. Twelve patients had 5 or more anomalies, exclusive of the rectoanal one. One patient had 10 other anomalies. Nine patients had congenital heart defects and 8 had a tracheoesophageal fistula.

SYMPTOMS AND PHYSICAL FINDINGS

The Type I malformations are discovered at varying periods of time post partum, depending upon the degree of stenosis present. The child experiences difficulty with defecation, may pass ribbon-like stools, and frequently has abdominal distention. Examination reveals a normal anus with a stricture 1 to 4 cm. above the anal orifice. The Type II and III anomalies are discovered by routine examination, failure to pass meconium, and by the nurse attempting to insert a thermometer. The presence of a perineal or vaginal fistula large enough for evacuation of meconium sometimes causes delay in discovery of the abnormality. Passage of meconium or air per vagina, urethra, or through abnormal perineal openings is evidence of the presence of a fistula and suggests location. In any male child with a Type III anomaly, a rectourinary tract fistula should be strongly suspected. Urinalysis for meconium may establish the diagnosis. Any external opening can be probed or injected with contrast media to determine the level of the rectal pouch. Puckering of the anal dimple on stimulation gives indication of sphincter action. The Type IV cases show signs and symptoms of intestinal obstruction. Diagnosis is often delayed by the presence of a normal anus. Obstruction is met when a probe or catheter is inserted into the anus.

DIAGNOSIS BY ROENTGENOGRAPHY

Wangensteen and Rice[28] made a very valuable contribution when they described a method of taking roentgenograms of the infant in the inverted position. The purpose of this method is to allow the gas to rise to the termination of the rectum and indicate the distance between the skin and end of the rectum. Berman[2] advocates this method but points out the fallacy of x-ray before 24 hours, since he believes that gas rarely goes beyond the hepatic flexure before this time. Others[15, 18] agree with this modification of the Wangensteen-Rice method. Lee[16] massaged the abdomen to help the gas to

traverse the gastrointestinal tract more quickly. Other important roentgenographic methods consist of injection of fistulas with iodized oil and insertion of barium or iodized oil through the distal segment of a colostomy. Thompson[25] feels that cystography and voiding urethrograms are important in males. Hamm and Harlin[10] add that injection of dye as the catheter is pulled through the urethra may show up a urethral fistula. Kiesewetter[14] believes that most fistulas do not show up with cystography but that excretory urography should be carried out before the child leaves the hospital because of the incidence of associated kidney abnormalities.

TREATMENT

The Type I cases are usually successfully treated by repeated dilatations. Type II cases require cruciate incisions to perforate the thin diaphragm occluding the anus. This procedure should be followed by frequent dilations to prevent constriction by scarring. The mother can do this daily at home with her small finger.

In dealing with Type III imperforate anus, a careful evaluation must be made preoperatively regarding distance of the blind end of the rectum from the anal skin, associated anomalies, and presence of fistulas. A definite plan should then be formulated before operation is begun. If the blind end of the rectum is within 1.5 cm. of the anal skin, repair can be done satisfactorily through a perineal approach. A longitudinal incision is made over the anal dimple, transecting the anal sphincter. The blind end of the rectum is identified and the rectum is mobilized sufficiently to suture the terminal rectum to the skin without tension. If the blind end of the rectum is above 1.5 cm. from the anal skin, the perineal approach should not be utilized.

In 1948 Rhoads, Pipes, and Randall[22] described a one-stage abdominoperineal operation for cases in which the colon cannot be reached safely through the perineum. Many others have followed in the use of this procedure. This operation has been used to greatest advantage in Type III cases with a rectal pouch above 1.5 cm. and when associated with a rectovesical or rectourethral fistula. The abdominoperineal operation is well described by Rhoads and co-workers,[22] Norris and associates,[18] Santulli,[23] Butcher,[5] Potts,[20] Kiesewetter,[14] and Gross.[9] The advantage of this procedure is that the imperforate anus as well as any associated fistulas can be repaired at one time. The recurrence rate of rectourinary fistulas is greatly reduced because normal bowel wall lies adjacent to the closure of the urinary end of the fistula. The anal sphincter is dilated and preserved. It carries the possible disadvantage of neuromuscular weaknesses. Wallace and Colvin[27] warned that a catheter should be placed in the male urethra for identification and splinting. Poth, in discussing an article by Thompson,[25] stated that urine entering the bowel freely can cause a metabolic acidosis of a serious degree, thereby citing another reason for early repair of rectourinary tract fistulas.

The treatment of imperforate anus with rectoperineal and rectovaginal fistulas should be delayed if the opening is adequate or can be made so by dilation for satisfactory evacuation of bowel contents. Santulli[23] feels that

any fistula should be repaired at any age if it is too small for adequate evacuation, if there are repeated episodes of fecal impaction or repeated episodes of ascending urinary tract infection. Repair is accomplished by a perineal approach if the fistula is a low-lying one. If the fistula is high, an abdominoperineal approach would be necessary. If treatment can be delayed, Potts[20] and Hanley[11] do a definitive repair in the first few weeks after birth whereas Kiesewetter[14] advocates waiting until the child weighs 20 to 25 pounds. Santulli[23] corrects them at 3 to 12 years of age. Gross[9] is critical of dilating fistulas unless the child is in precarious condition and operation is hazardous. The operative technique for the perineal operation is described in detail by Gross,[9] Hanley,[11] Potts,[20] and Santulli.[23]

Type IV cases are treated very much like the Type III cases. Unfortunately, many of these are recognized late and only after the infant's abdomen has become distended. If the condition is precarious, only a colostomy should be used. Gross[9] recommends abdominoperineal pull-through as the best method of definitive correction.

Transverse colostomy has its place in infants weighing less than 6 pounds, in those showing evidence of some other serious anomaly, and in those appearing in poor condition at birth. Definitive correction can be made when the child is older and a better operative risk. Mayo and Rice[17] performed 65 colostomies in 165 patients and found that 22 (33.8 per cent) of those having a colostomy had trouble with the distal loop. This consisted of impacted feces, barium concretion, and prolapse or retraction of the distal barrel. Therefore they warned that these colostomies should be carried out very carefully and that the 2 barrels should be separated.

RESULTS OF TREATMENT

Forty-three cases of imperforate anus were treated at the University of Michigan Hospital from January, 1950, through June, 1955. Only these cases will be discussed in regard to treatment and results since this group was treated in the era of antibiotics and after newer concepts of repair had been initiated. Eight of the 43 cases had operative procedures done in outside hospitals prior to admission. The type of treatment is presented in Table III.

TABLE III

OPERATION	NUMBER CASES	DEATHS
Perineal repair only	19	2
Colostomy only	11	8
Abdominoperineal repair	2	
Abdominoperineal repair and colostomy	2	
Perineal repair and colostomy	1	
No operation	8	4
	43	14

Perineal repair only was done for 3 cases of Type II and 16 cases of Type III imperforate anus. One of the Type III group had a rectovaginal fistula and 11 had a rectoperineal fistula.

Colostomy was performed in 8 instances because of other severe congenital anomalies. A rectourinary tract fistula was the indication in 2 other cases, while

an unsuccessful attempt at repair of a rectourinary tract fistula made prior to admission was the indication in one case.

The 3 cases having colostomy in addition to another procedure had had unsuccessful attempts at correction prior to admission.

No operation was performed on 8 patients because of other severe anomalies in 5, parents' refusal and adequate fistula in 1, functioning colostomy in 1, and fairly adequately functioning perineoplasty in 1.

There were 14 deaths in these 43 patients, a mortality of 32.6 per cent. Thirteen of these deaths were in patients having other severe congenital anomalies, and in each case the death was believed to be due to the other anomaly. Only one death was due to the imperforate anus alone. This was a Type III patient with rectourinary tract fistula who had had an unsuccessful attempt at repair prior to admission.

Twenty-five patients survived operation. The type of operation and the early operative results are given in Table IV. At the time of this report it was too early to evaluate these patients from the standpoint of bowel and urinary status. It is hoped that that can be accomplished in another report. A satisfactory result is one in which the anal opening was adequate for normal evacuation. An unsatisfactory result is one in which the opening is inadequate and complicated by impactions or fecal incontinence, provided the child was old enough to exert some bowel control.

TABLE IV

OPERATION	NUMBER OF CASES	SATISFACTORY	UNSATISFACTORY
Perineal repair	17	16	1
Colostomy	3	Definitive repairs deferred	
Abdominoperineal repair	2	2	
Abdominoperineal repair and colostomy	2	1	1
Perineal repair and colostomy	1		1
	25	19	3

All of the 3 unsatisfactory results were complicated by unsuccessful attempts at correction prior to admission.

CONCLUSIONS

1. Inadequate initial treatment gives very poor results.

2. Imperforate anus is associated with a high incidence of fistulas and other congenital anomalies.

3. A careful evaluation must be made preoperatively regarding the distance of the blind end of the rectum from the anal skin, associated anomalies, and presence of fistulas.

4. A definite plan should be formulated before operation is begun.

5. If the blind end of the rectum is within 1.5 cm. of the anal skin, repair can usually be accomplished satisfactorily through a perineal approach.

6. If the blind end of the rectum is separated from the anal skin by more than 1.5 cm., repair through an abdominoperineal approach should be strongly considered.

7. Transverse colostomy has its place in infants weighing less than 6 pounds, in those showing evidence of other serious anomalies, and in those appearing in poor condition at birth.

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DUPLICATION OF THE STOMACH

A Report of Two Cases in Infants

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DUPLICATIONS are among the more rare anomalies of the alimentary tract. When only those originating from the stomach are considered, the number of cases reported is still further reduced. According to a recent author only 28 cases have been reported so far in the English Literature.[5] Although these are congenital anomalies the symptoms often are not evident until adult life.[6, 11] Two cases recently encountered in infants form the basis of this report.

CASE REPORTS

Case 1.—N. L., an 18-day-old first-born female, was admitted to the U. S. Naval Hospital, Chelsea, Massachusetts, on Jan. 27, 1955, with a chief complaint of 3 days' vomiting.

Present Illness.—Three days prior to admission the child started vomiting. The vomiting occurred immediately following feedings. It was projectile and not bile stained. The mother discontinued breast feeding and placed the child on an evaporated milk formula. One day later the child was seen in the Outpatient Clinic, and there was given feedings of sugar water alone by mouth. In spite of this the vomiting continued.

Maternal History.—There were no maternal illnesses in the first 2 trimesters of pregnancy. Seven weeks prior to delivery the mother was operated upon for acute appendicitis. The paternal grandmother had diabetes.

Physical Examination.—The patient was a well-developed, well-nourished female infant somewhat dehydrated and irritable but alert. The weight was 6 pounds 8 ounces. The abdomen was soft; there was a 2 by 2 cm. freely movable tumor palpable in the right upper quadrant and periastaltic waves were observed crossing the epigastrium from left to right.

The child was prepared for surgery. The preoperative diagnosis was hypertrophic pyloric stenosis.

Operative Note.—A transverse incision was made in the right upper quadrant. On the greater curvature of the stomach close to the pylorus, a tumor was present. It was intramural, firm, and corresponded in size to what had been felt on palpation. The pylorus itself was entirely normal. The tumor was excised locally. It did not extend through, but down to, the mucosa which could be left intact. Rather than compromise the lumen of the antrum by closure, the wound was left open with the mucosa bulging out as in a Ramstedt pyloroplasty.

Postoperative Course.—Feedings by mouth were started 12 hours postoperatively and were well tolerated. Save for a wound infection caused by hemolytic *Staphylococcus aureus*, the child made an uneventful recovery and was discharged from the hospital 4 weeks later, at that time weighing 7 pounds 1 ounce.

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Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Case 2. Roentgenogram of chest. The heart is displaced to the left. The tumor extends into the right pleural cavity and appears to indent the diaphragm in the midline.

Fig. 2.—Case 2. Roentgenogram of chest, lateral view. Contrast material in the esophagus outlines the anterior border of the tumor.

Fig. 3.—Case 2. Roentgenogram of chest. Postoperative appearance of anteroposterior view.

Pathologic Examination.—"Specimen consists of a whitish partly encapsulated mass measuring 1.3 cm. in diameter. On section there is a central lumen about 2 mm. in diameter containing mucus."

Microscopic Examination.—"The central lumen is lined by mucosa composed of simple branching tubular glands. The cells are mucus-producing and have basally placed nuclei. In some areas there is no gland formation, and the lining consists of a simple layer of columnar and cuboidal cells. The muscular walls vary in thickness. In areas there is muscularis mucosae and 2 distinct layers of muscle bundles at right angles to each other. In other areas the mucosa reaches almost to the serosa with only a few fibers separating the two. In the thicker part of the wall there are numerous areas of pancreatic tissue."

Comment.—The diagnosis of hypertrophic pyloric stenosis in this child seemed obvious in spite of its being a female. The correct diagnosis was only made at operation.

Other authors have reported difficulty in performing local excision of duplications in this location and have resorted to partial gastric resection.[2, 8]

The difficulty here was overcome by not closing the muscle layers as the mucosa itself was intact.

CASE 2.—L. B., a 4-week-old female, was admitted to the U. S. Naval Hospital, Chelsea, Massachusetts, from another military hospital on Jan. 24, 1957, with the diagnosis of a mediastinal cyst. The infant had been born at term following a normal pregnancy. Birth weight was 7 pounds 6 ounces.

Present Illness.—At the age of 3 weeks the child became listless, refused feedings, and seemed to have trouble breathing. On admission to the referring hospital, the child was cyanotic with shallow respirations. There was dullness over both lung fields, with diminished breath sounds and crepitant râles on the left side and decreased-to-absent breath sounds on the right. Roentgen examination of the chest revealed a mass apparently continuous with the heart extending into both lung fields. Shortly after admission respirations ceased and heartbeat could not be detected. Adrenalin (0.1 c.c. of a 1:1,000 solution) was given subcutaneously and, when no effect was seen, the needle, wet with adrenalin, was plunged into the heart muscle through the chest wall. There was immediate resumption of the heart action which settled into a regular rhythm after 3 or 4 minutes. Respirations were maintained by manual pressure on the rib cage and subsequently returned to normal. The diagnosis of congenital heart disease was entertained. The child was digitalized and given oxygen.

However, no improvement was noted. Roentgen examination with contrast material in the esophagus revealed this to be displaced anteriorly and to the left. Following this examination it was felt that a mediastinal cyst could be present and, as the child appeared moribund, a thoracentesis was carried out just inferior to the angle of the right scapula. About 90 c.c. of fluid, mucous in character, was aspirated and a dramatic improvement in the child's condition occurred. Breath sounds could now be heard over both lung fields with only occasional râles on the left. At this point the child was transferred to this hospital for definitive treatment.

Examination on arrival revealed a fairly well-nourished white female child with slight circumoral cyanosis. There was dullness over the right lower lung field with diminished breath sounds. The heart was not enlarged; there was normal sinus rhythm, no murmurs or thrills present.

Roentgen Examination of the Chest.—"There is a circular mass approximately 5 cm. in diameter in the right posterior thorax. The heart appears to be displaced to the left. Barium contrast study reveals the esophagus to be displaced anteriorly and to the left."

The patient was prepared for surgery. The preoperative diagnosis was either a duplication of the esophagus or a neuroblastoma.

Operative Note.—The chest was opened on the right side through the sixth intercostal space. There was a cystic mass 6 by 8 cm. in size in the right posterior mediastinum displacing the esophagus anterior and to the left. The mass was easily dissected free from the mediastinal structures. There was no connection to the vertebral column. The cyst was traced

down through the esophageal hiatus and found to be connected to the lesser curvature of the stomach by fibrous tissues about 2 cm. below the esophagogastric junction. It was removed intact.

Postoperative Course.—The child made an uneventful recovery and was discharged from the hospital 10 days after the operation.

Pathologic Report.—"The specimen consists of a cystic structure, somewhat pear-shaped and measuring 3 by 3.5 by 2 cm. (specimen fixed in formalin). The outer surface is shaggy and irregular. On multiple cross sections, the wall of the cyst is seen to be 0.3 cm. in diameter and to have an inner lining that is tan in color, measuring approximately 1 mm. in thickness, surrounded by a greyish-white muscular wall. The material in the cyst is dirty brown and bloody."

Microscopic Examination.—"The cyst wall is composed of 2 layers of smooth muscle; one circular, the other at right angles, longitudinal. Some muscle bundles appear to run obliquely. There is a muscularis mucosae and the mucosa is composed of straight glands, dividing in two, rather deep in the mucosa forming simple branched glands. Zymogenic cells are seen in the deeper parts of the branched glands."

Comment.—This duplication in the chest projected into the right pleural cavity. This is the rule, as most of these lesions develop in the dorsal mesogastrium, and when the rotation of the stomach to the left occurs this position is assumed. Symptoms may be quite varied and simulate any space-occupying lesion in the posterior mediastinum. There is even a report on one such cyst being drained as an empyema before the true nature was discovered.[9] Occasionally hemorrhage or perforation occurs from the acid-peptic juice secreted by the duplication.[3, 4, 7] The bloody contents in this case were explained by the aspiration performed preoperatively and handling during operation.

DISCUSSION

Both of the lesions removed were lined with gastric mucosa and had an intimate connection with the stomach. Because of this we have classified these as gastric duplications although, according to some authors, the duplication does not have to possess mucosa identical to the adjacent organ.[4] Several theories have been offered to explain the formation of these and similar anomalies. Bremer[3] has stated that the gastric lumen does not go through successive stages of obliteration by epithelial proliferation and subsequent recanalization by growth in length and vacuolation, as does the esophagus and duodenum along with most of the intestinal tract.

If one accepts Bremer's statement, the most plausible explanation of intestinal duplications cannot be applied to the stomach. He explains some gastric duplications, especially along the greater curvature side of the stomach, on the basis of fusion of longitudinal mucosal folds, this occurring during the second and third months of fetal life. If this explanation is true, all layers of the normal stomach wall should be found in the duplication. Lewis and Tyng (cited by Bremer[3]) explain duplications on the basis of mucosal diverticula of the gastrointestinal tract observed in the human embryo. Cases formed according to this theory could only have at most one muscular layer in their wall. Our first case should presumably be explained according to this theory as the wall of the duplication on the serosal side was only one muscle layer. The presence of gastric duplications inside the thorax is explained by McLetchie[7] and before him, Bell,[1] by a persistence of the neurenteric canal, in this case between a gastric diverticulum and the spinal cord, usually in the lower cervical or upper thoracic region.

In many of the cases quoted by these authors an anterior spina bifida along with a gastric duplication or diverticulum was present. The gastric lesion was attached to the spinal cord or vertebral bodies by a cordlike structure. The spina bifida and the connecting structure should be prerequisite to making this diagnosis. Neither of these was observed in the case under discussion.

Fig. 4.

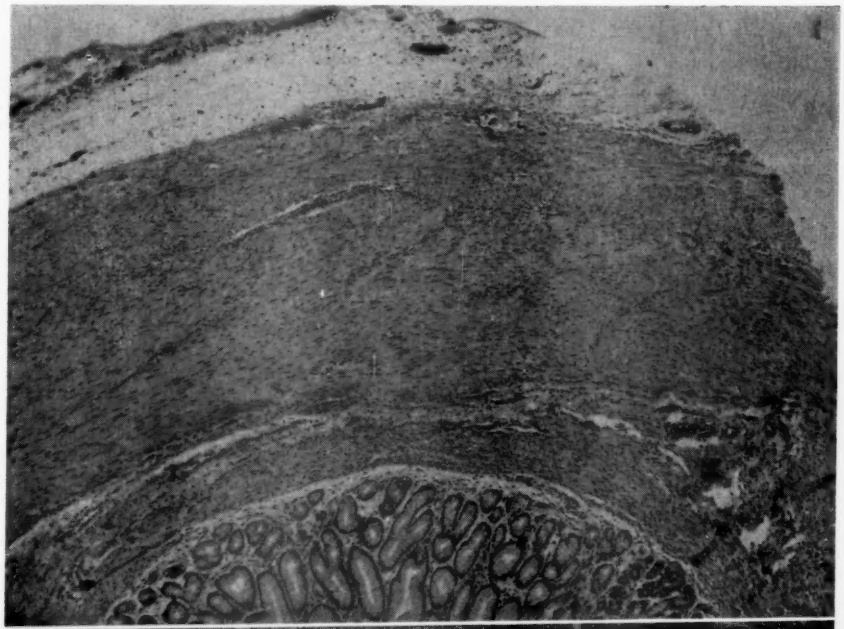

Fig. 5.

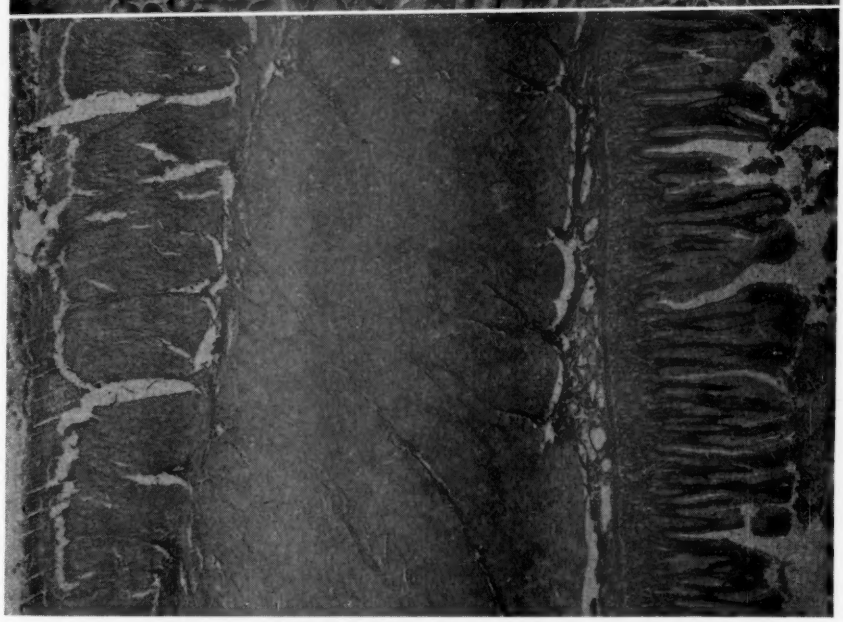

Fig. 4.—Case 1. Microscopic appearance of wall of intramural duplication. Between the serosa and mucosa there is only one muscle layer. In other areas this layer is quite thin. (Hematoxylin and eosin, ×50).

Fig. 5.—Case 2. Microscopic appearance of wall of thoracic duplication. There are two well-developed muscle layers, one at right angles to the other. The thickness and arrangement of these layers is fairly uniform throughout the duplication. (Hematoxylin and eosin, ×25).

When considering the explanation of thoracic gastric duplications it should be kept in mind that in early fetal life the stomach is an intrathoracic organ. According to Patten,[10] at the end of the first month of fetal life the dilatation of the foregut which later becomes the stomach is located in the thorax posterior to the heart. It is only during the second month that the stomach moves into the abdominal cavity or to the location which later is inside the abdominal cavity. Assuming that the duplications in question are formed prior to the descent of the stomach, it is only logical to think it possible for these malformations to become separated from the mother organ and stay in their original location.

SUMMARY

Two cases of gastric duplications in female infants are presented. One of these was intramural near the pylorus. The other was intrathoracic, projecting into the right pleural cavity. Symptoms were, in the first case, those of pyloric obstruction mimicking hypertrophic pyloric stenosis. In the second case, the symptoms were mainly respiratory in nature. Both lesions were treated by local excision, preserving the continuity of the alimentary tract without resorting to resection. Both infants survived and left the hospital in good health.

A short discussion of theories pertaining to etiology is appended.

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Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

MANAGEMENT OF PERFORATED PEPTIC ULCER

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CONTEMPORARY policies regarding the treatment of acute gastroduodenal perforations are surprisingly divergent. Since 1919 when Von Haberer first recommended emergency partial gastrectomy for this situation, a large and increasing experience with this procedure has developed in Europe. Recently, many American surgeons have adopted this policy of simultaneous operative control of the ulcerogenic mechanism and of the perforation. In England, Taylor[6] elaborated the method of treatment without operation, using continuous gastric aspiration to maintain self-sealing of the perforation. Seeley,[5] in the United States, has shown impressive results with this technique. In contrast to the foregoing, the majority of American surgeons believe that the standard policy should involve an operative procedure that is restricted to closure of the perforation.

Our appraisal of the foregoing involves a critical presentation of the current methods of management used on the University of Southern California service of the Los Angeles County Hospital. From 1940 to 1958 there were 2,154 cases of perforated peptic ulcer diagnosed at this hospital; 1,854 were duodenal, and 298 were gastric. Simple closure of the perforation was the usual method of treatment. The annual operative mortality varied from 5 to 20 per cent with an average of 10.9 per cent for those treated surgically. For the patients under 50 years of age the mortality was approximately 4 per cent, and for those over 60 years of age it was approximately 16 per cent. The sharp rise in mortality after the fifth decade parallels a similarly increased mortality in patients whose treatment is delayed more than 12 hours.

The greater lethality of gastric ulcer as compared to duodenal ulcer perforations is presented in Table I. Gastric ulcer seldom occurs in the younger age groups. The high frequency of chronic alcoholism, malnutrition, old age, concurrent disease, and late admission after perforation causes great complexity in management of acute perforations of peptic ulcer in a large municipal hospital.

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TABLE I. DEATH DUE TO PEPTIC ULCER IN 31,057 NECROPSIES

Gastric ulcer	
Perforation	124
Hemorrhage	113
Duodenal ulcer	
Perforation	208
Hemorrhage	117

However, these features also provide unusual opportunity for utilizing, in varying circumstances, all of the described methods of treatment. Our current policies in adapting treatment to this varied material will be presented in conjunction with a discussion of each of these methods.

ACUTE PERFORATION OF ACUTE ULCER

The precepts responsible for the existing divergent opinions regarding therapy constitute the basis for the individual surgeon's judgment in developing his own therapeutic policy. A key consideration involves the surgeon's opinion of the importance of acute duodenal ulcer. Taylor[6] has good evidence that acute duodenal ulcer is common in his area, that perforations of such ulcers are small and seal uniformly with gastric suction, and that chronic duodenal ulcer usually is not a sequel. Substantiation of Taylor's opinion is provided by Gilmour[2] of Newcastle-on-Tyne. Basing the diagnosis upon operative findings, he has shown that, in a series of 206 cases of perforation treated surgically, 119 cases were perforations due to acute ulcer. There was no mortality in this acute ulcer group, and less than 10 per cent required surgery at a later date. Here pathologic proof has been provided to substantiate the conclusions of Taylor who based his diagnosis of acute ulcer upon a history of preceding dyspepsia of less than 3 months' duration. Further, in his cases, these ulcers healed and chronicity seldom developed.

Follow-up studies in the United States show that approximately 30 per cent of patients do well following simple suture of perforated ulcer. Many of this group could represent cases of acute ulcer with acute perforation. If partial gastrectomy were done for all cases of gastroduodenal perforation without excluding perforations of acute ulcer, a large portion of the 30 per cent might have been done for perforation of an acute ulcer. It may be that acute ulcer is more common in England than in the United States. Regrettably, most present-day reports from the United States do not distinguish between perforation of acute ulcers and of chronic ulcers. We believe such a distinction should be made. It should be noted that, although Taylor has used a history of less than 3 months of dyspepsia as a basis for the diagnosis of acute ulcer, others have found that some patients who give a negative antecedent ulcer history at the time of admission will give a positive history during recovery. Therefore, the historical criteria of chronicity should be a combination of preoperative and postoperative interrogation. Of equal importance are the operative findings which should be included in the determination of chronicity. The place of acute ulcer in the total problem remains to be

settled; but we are as much indebted to Taylor for emphasis upon the importance of acute ulcer as we are for his development of aspiration therapy and demonstration of the frequency of self-sealing of acute perforation.

INTRAGASTRIC SUCTION TREATMENT

Clarification of the role of intragastric suction in the management of gastroduodenal perforation is necessary. Actually there are 4 situations in which it is used; in two it constitutes definitive treatment, and in two it is adjuvant therapy. As definitive treatment, suction, in place of surgery, is used as prescribed by Taylor and by Seeley[5] for operable cases. Second, it is used electively by many surgeons as basic treatment for cases considered inoperable, either because of advanced duration effects of the perforation or because of severe concurrent disease. As adjuvant treatment, gastric suction is employed partially for its value in preventing reperforation during the early postoperative period following simple suture. Such early reperforation accounts for a portion of the mortality following simple closure of larger perforations. As a second adjuvant, gastric suction is used in the management of formes frustes perforations. Here, as in the operative cases that have been treated by simple suture, gastric suction is believed to be of value in preventing reperforation. However, there is little supportive evidence based upon controlled studies. The foregoing distinctions should be followed in the reporting of groups of cases as nonoperative, and, especially, moribund cases should be separated since from a therapetuic standpoint moribundity is the equivalent of death.

Suction treatment, as used electively by Taylor and Seeley, has created great interest because of the amazingly high percentage of successes obtained with the method. The accepted explanation for these beneficial effects is that effective suction prevents leakage of gastric contents from both gastric and duodenal perforations. In this regard we have been impressed by the fact that, paradoxically, bile is usually absent in the peritoneal fluid of perforated duodenal ulcer. Although absence of bile is difficult to understand, it would seem to validate the assumption that the major feature of the leakage problem in perforated duodenal ulcer is the leakage of gastric content alone rather than of material from the duodenum and the structures draining through the papilla of Vater. However, even though these concepts regarding the mode of action of gastric suction are probably correct, they do not preclude consideration of the possible value of duodenal suction such as would be provided by advancing the Levin tube through the pylorus. In cases where leakage has been so severe that the systemic effects contraindicate surgery, duodenal-gastric suction might be superior to gastric suction alone.

There are certain differences in the recommendations of Taylor and Seeley, both of whom favor suction treatment for perforated ulcer. The former advises suction treatment if there has been less than 3 months of dyspepsia, immediate gastrectomy if the dyspepsia is of more than 3 months' duration, and simple closure if established peritonitis exists. The total mortality in Taylor's series of cases was 11 per cent. For the group treated by

aspiration the mortality was 2.5 per cent. Seeley recommends suction treatment for all patients. Mortality in his group of patients was 5 per cent. Approximately one-half of the deaths were in patients moribund on admission. In this entire series all but 4 cases were duodenal perforations and only 9 patients were 60 years of age or older. These two factors indicate that unusually favorable clinical material was used; however, it is extremely impressive that in only one instance was it apparent that death occurred from failure of the perforation to seal.

From the foregoing, it seems tentatively established that, if in England, gastric suction is used for acute perforations in patients with a very short history of dyspepsia or, in the United States, in a predominantly young age group, a very low mortality should be obtained. The results in an older age group, in the United States, have not been well established. Additionally, in comparable groups of cases, the evidence does not indicate that the mortality with operative treatment is higher than with suction therapy. This is substantiated by Gilmour's report[2] of 119 perforations of acute ulcer treated surgically with no deaths.

Important factors handicap suction treatment. The method requires great diagnostic judgment, skill, and a very large amount of continuous observation by the attending staff. Its advocates do not exclude from its use the 20 per cent of patients with acute perforation in whom x-ray studies fail to show pneumoperitoneum. In this group there are many possibilities for mistakes in diagnosis and in management of surgical lesions simulating perforated ulcer, especially in older patients. Additionally, suction treatment eliminates ulcer-curative surgery for the ulcer disease at the time of the acute perforation. An even greater objection than the foregoing is the lack of positive control of the perforation. By utilizing the operative method the lesion can be seen and closed in a positive manner, and to a great degree the danger of leakage can be avoided in any case that might not have sealed and remained sealed on aspiration alone. Even with a negative antecedent history, many perforations are large and are due to chronic ulcers. These probably do not seal without surgery as frequently as do the small perforations of acute ulcers.

More frequent use of gastric aspiration in operable cases of perforation will occur when it is possible to identify self-sealing more precisely than by Taylor's method. At present self-sealing is implied when the diagnosis of forme fruste perforation is made. This diagnosis also implies that peritoneal irritation is minimal. Because it includes two variables, this diagnosis is objectionable. Self-sealing can coexist with active peritoneal irritation, with subsiding peritoneal irritation, and with minimal peritoneal irritation. At present both of the latter two groups can and should be identified and treated conservatively. It may be possible to develop a method for proving the true situation in the group in which active peritoneal irritation still exists but in which sealing has occurred. We are studying this possibility by administering through the Levin tube, during the roentgenographic study before surgery, both methylene blue and Gastrografin, a radiopaque fluid. Correlation between the presence or absence of leakage in the film and the dye distribution

at the time of surgery may establish that the Gastrografin study will satisfactorily serve to establish the presence or absence of sealing. Increased recognition of the cases of sealed perforation is a clear responsibility and offers significant advantages to such patients.

CONCURRENT CURATIVE PROCEDURES FOR CHRONIC ULCER AND PERFORATION

Steadily increasing evidence is available from an enlarging number of follow-up studies regarding the prognosis following recovery from gastroduodenal perforation. As the accuracy and length of follow-up period of these reports increase, a progressively larger number of patients are found to present recurrent ulcer disease, and a similarly progressive increase is found in the numbers requiring subsequent partial gastrectomy. Many good studies indicate that 80 per cent of perforation survivors will have subsequent important ulcer trouble and that at least half of these will require curative surgery. Certain reports indicate that as many as 60 per cent of the survivors will require secondary operation, and in other studies nearly 80 per cent required later gastrectomy. In these reports there is usually no distinction between the gastric and duodenal perforations and between acute and chronic ulcers. Gilmour reported pathologic differentiation between acute and chronic ulcer at the time of simple suture. In this series all of the perforated chronic ulcers subsequently presented serious ulcer disease.

The greatest problem for the proponents of emergency gastrectomy is to avoid this procedure in those patients who would not subsequently need it. In some recent studies the proportion of such patients approaches 50 per cent. This phase of the problem has been met by establishing criteria for gastrectomy aimed at selection of those patients who almost certainly will require later ulcer-curative surgery. Follow-up studies of patients who meet such criteria but who are treated by simple suture would very much clarify this problem and might establish that when these criteria are followed a very low incidence of unnecessary gastrectomy would result. At least, until such a study is completed, emergency gastrectomy will be opposed seriously on the basis that it will, if used routinely, subject 30 per cent of such patients to unnecessary gastrectomy, and especially because 15 per cent of these probably would have important postgastrectomy disturbances. There is general agreement that the basic requirements necessary for consideration of emergency gastrectomy include a surgeon skilled in gastrectomy, a highly qualified anesthesiologist, and a good-risk patient with an early perforation. These, of course, merely assure a low mortality rate. Further, they raise the percentage of poor results in excluded cases. A very complex problem arises over the contention that the mortality rate may be reduced by more frequent use of gastrectomy. At present we believe that where this has occurred, adjuvant therapy has been inherently emphasized in the gastrectomy group as compared to cases not so treated. There are special situations such as associated bleeding, multiple ulcers, or very large perforation where gastrectomy would conceivably carry a lower mortality than simple suture. It seems a

reasonable conclusion that ulcer-curative surgery is justified in those cases where the presence of progressive chronic ulcer disease is almost certainly established by history and operative findings. We do not believe that perforation itself is necessarily an indication of ulcer virulence. Transmural ulceration probably occurs in posterior duodenal ulcer as quickly as in anterior duodenal ulcer. In both groups, penetration after development of chronic symptoms does no more than confirm progression. When the basic permissive factors exist, there should be less rigid indications for gastrectomy for gastric than for duodenal ulcer. The possible presence of carcinoma, the probability that medical treatment for gastric ulcer is less satisfactory than for duodenal ulcer and that perforated acute gastric ulcer is uncommon, and the comparative simplicity of the gastrectomy done for gastric ulcer justify the less stringent indications.

Last, it seems cogent to point out that, in any given case where death occurs following gastrectomy and simple suture might have been used, a very saturinine load has been placed upon the surgeon's conscience.

CONDITIONS BY WHICH THE DESIRABILITY OF ULCER-CURATIVE SURGERY IS JUDGED

We have accepted the principle that, if sufficient evidence of progressive ulcer disease exists in a given case, ulcer-curative surgery may be justified as an emergency procedure. We analyze the problem on the basis of 4 types of conditions: (1) those assuring that the patient will tolerate the procedure, (2) those indicating chronicity of the ulcer, (3) those indicating the presence of progressive ulcer disease, and (4) those unfavorable to a successful result from simple closure.

1. Conditions assuring patient's tolerance of ulcer-curative surgery (all conditions must be present):
   a. Perforation of less than 12 hours' duration.
   b. Good-risk patient, no serious concurrent disease.
   c. Experienced surgeon and anesthesiologist.
   d. Uncompensated shock not present at time of admission.
2. Conditions assuring chronicity of the ulcer (one must be present):
   a. Pathologic character of the tissues must indicate chronic ulcer.
   b. Important symptoms of ulcer have been present for at least 6 months.
3. Conditions indicating the presence of progressive ulcer disease (one condition in group 3 or 4 must be present):
   a. Previous perforation or hemorrhage.
   b. Pyloric obstruction.
   c. Perforation occurring while patient is on good medical regimen.
   d. Patient cannot procure or will not follow adequate medical regimen.
   e. Patient requires steroid therapy but has not recently been on large doses.
4. Conditions unfavorable to successful result from simple closure:
   a. Secure closure of the perforation not technically feasible
   b. Associated hemorrhage
   c. Multiple ulcers
   d. Suspicion of carcinoma

Delayed curative surgery following convalescence is recommended for patients in whom curative surgery was indicated at the time of perforation but whose condition permitted nothing more than simple closure. Emergency gastrectomy is recommended for all our patients with gastric ulcer when ulcer-curative surgery is to be performed. However, for perforated duodenal ulcer we usually utilize pyloroplasty and vagotomy. This latter procedure carries a lower mortality than gastrectomy, the physiologic sequelae are less important, and, if the surgeon is experienced in performing a complete vagotomy, the curative results are as good. Mediastinitis has not occurred in our experience.

SIMPLE CLOSURE OF PERFORATION

The basic problem in management of gastroduodenal perforation is to eliminate the perforation. The simplest positive means of accomplishing this is by direct suture. The inherent lethality of this operative procedure has been proved to be nearly zero when optimal conditions are encountered. Therefore, we believe that simple suture constitutes the basic method for treatment of acute perforations. Other forms of treatment are available for selected situations, but these should be chosen only with the greatest wisdom. Further, simple closure, because it requires laparotomy, provides the potential for salvaging situations where the lesion is surgical but has been misdiagnosed as a gastroduodenal perforation.

In accomplishing simple closure, chromic catgut on an atraumatic needle should be used to place the interrupted sutures. Nonabsorbable suture material should be avoided. The closure should be transverse. Technical difficulties may occur. If the perforation is sizeable and considerable fixation of calloused tissue is present, a through-and-through layer of catgut should be placed and then a seromuscular row if this is possible. A very large duodenal perforation presents an extremely difficult problem. Reperforation is a distinct hazard. Lateral duodenal fistula from such a reperforation presents difficulties that we have failed to solve satisfactorily. Pyloroplasty permits satisfactory closure in some large perforations, but gastrectomy of the Billroth II type is probably the best possible solution for large perforations. Catheter duodenostomy can be used to meet the problem of duodenal closure if the duodenal stump cannot be closed satisfactorily. Occasionally, when simple closure seems precarious, but not enough so to justify gastrectomy, temporary gastrostomy with a catheter, the tip of which is passed through the pylorus, will provide a means of continuous suction to the duodenal as well as the gastric lumen and thus reduce the chance of reperforation.

Obstruction of the lumen may be produced by simple closure of juxtapyloric ulcer perforations. However, it does not occur often and the need to reoperate upon patients for postoperative pyloric obstruction arises even less frequently. Nevertheless when the surgeon is convinced that obstruction will be produced by simple closure, pyloroplasty or gastrectomy is indicated.

Reperforation in the first few days after simple closure is a complication that usually results fatally. When it has happened on our service, either the

closure has been difficult or the patient has been extremely malnourished. Braun of Leipzig published the first case of successful simple closure in which omentum was grafted over the perforation. Thompson[7] showed that, among a large group of cases at the Los Angeles County Hospital, mortality was importantly reduced when simple closure was reinforced by a living omental graft. If there is reason to suspect that reperforation will occur, such a living tag must be sutured over the closure.

DIAGNOSIS OF GASTRODUODENAL PERFORATION

The typical case of gastroduodenal perforation is readily recognized. Perhaps 10 per cent of cases are atypical. If proper roentgenographic studies are made, the presence of pneumoperitoneum can be demonstrated in about 80 per cent of all cases of acute perforated ulcer. It is our practice to routinely procure the standard abdominal scout film (dorsal decubitus with film posterior and rays vertically downward) and a lateral decubitus film (right side up, rays horizontal) of all patients with suspected acute abdominal lesions in whom the clinical diagnosis is not clear and definite. In the atypical cases of perforation, the detection of free intraperitoneal gas will create a situation which resolves into a differential diagnosis of the causes of spontaneous pneumoperitoneum. Among these, perforated ulcer will be primarily considered. Frequent use of these two abdominal roentgenograms, whenever difficulty exists in making a satisfactory diagnosis of any acute abdominal lesion, also often will give evidence indicative of other conditions simulating perforated peptic ulcer. The right-side-up lateral decubitus film will reveal free intraperitoneal gas about as often as will an upright film of the diaphragm and additionally will reveal fluid levels and gas in the intestine and their characteristic patterns if they are present either due to paresis or mechanical obstruction. Free fluid may be suggested by the film when perforation is present without demonstrable pneumoperitoneum. It has been shown that in 8 per cent of gastroduodenal perforations, the ulcer can be outlined by reason of air in it. In radiologically difficult diagnostic problems, an upright film of the chest and left-side-up lateral decubitus film or a dorsal decubitus film with the rays horizontal may detect free gas not otherwise shown. It is perplexing that in the studies of large series, there is great uniformity of detection of pneumoperitoneum in about 80 per cent of cases of perforated ulcer. Why approximately 20 per cent in all series consistently fail to show free gas may have important implications, but we are unaware of any analysis of this special group. Actively leaking ulcer perforation may exist in the absence of pneumoperitoneum.

Elevated blood amylase levels occur in patients with perforated peptic ulcer. Mismanagement because of incorrect interpretation of the hyperamylasemia may create a situation in which death from perforated ulcer occurs in a patient being treated for acute pancreatitis. Hyperamylasemia increases in frequency and degree with increasing time after perforation and with increasing size of the perforation, and, therefore, cases with large, actively leaking perforations are the kind most likely to simulate severe pancreatitis. The cases of perforated ulcer with elevated amylase values but with

no free gas demonstrable by roentgenogram become extremely difficult diagnostic problems. Peritoneal tap is helpful in the diagnosis of both of these lesions. The fluid of perforated ulcer is turbid, and frequently smears will show organisms. Neither of these findings will be present in acute pancreatitis. Theoretically, when high contents of amylase exist in the free peritoneal fluid of perforated ulcer, this should be the result of flow from the papilla of Vater which has entered the duodenum and then drained into the peritoneal cavity through the perforation. In such problem cases the presence of bile in the peritoneal fluid obtained by tap is indicative of duodenal perforation. However, following ulcer perforation, we have observed that bile may be absent from the peritoneal fluid when its amylase content is high. Very high levels of amylase or the presence of blood in the peritoneal fluid have been shown by Hinton[4] to be diagnostic of pancreatitis. Mahaffrey[3] has reported that hyperamylasemia occurs in perforated ulcer cases only if the patient has ingested food or alcohol within 3 hours preceding perforation. In a difficult diagnostic situation, a leaking peptic perforation may be demonstrated by roentgenography using Gastrografin as a contrast media. The frequency of false-negative findings with this method is unknown.

SHOCK FROM PERFORATED PEPTIC ULCER

Shock is the most overlooked lethal factor in persons having acute perforation. Many surgeons have taught that these patients do not have shock. Although commonly misconstrued, this precept was intended to apply only to the onset of perforation when prostration simulates shock. Additionally, the doctrine that 12 hours after perforation the mortality rises sharply, further compounds the problem regarding shock. These teachings result in great efforts to rush the patient to the operating room. This does not harm the patient who is admitted very early after perforation. However, if perforation has produced much leakage and has existed for more than 6 hours, subclinical shock due to hypovolemia is almost certainly present. Compensatory vasoconstriction may mask this situation and maintain the patient in a normotensive state. Surgery without correction of hypovolemia, then, may, by virtue of blood loss and vasodilatation from anesthesia, be productive of severe shock.

During the past year, analysis of the postoperative deaths from perforated ulcer on our service at the Los Angeles County Hospital has revealed that shock had existed and had been inadequately treated before surgery. Patients with perforated ulcer, like those with any other surgical emergency, should have existing physiologic disturbances and blood volume deficits carefully determined and corrected before surgery. This should be accomplished without wasted time, but the specious concept relative to the rise in mortality after 12 hours should be ignored. Nasogastric suction should be instituted upon suspicion of the diagnosis of perforation. If the patient is then kept in the lateral decubitus position, right side up, further leakage should be minimal. With the patient in this position, the perforation will usually be near the top of the inverted U-shaped gastroduodenal loop. The necessary repletions can then be made without significant continuation of peritoneal injury.

Shock is probably the dominant feature producing the steep increase in mortality in patients above the age of 55 years. A reduced blood volume is characteristic of older persons who also have reduced vasomotor capacity to compensate for sudden hypovolemia. These patients are often admitted late following gastroduodenal perforations. These additional factors compound those previously indicated in the development of shock by perforated ulcer.

The major mechanism of the shock in perforated ulcer has been elucidated by Cope.[1] He concluded that the peritoneal injury from leakage is followed by extensive shift of plasma into the injured area. This resulted in hemoconcentration and decreased blood volume. These changes begin soon after perforation and continue for about one and one-half days even though leakage from the perforation has been controlled. He concluded that the amount of sequestration would not exceed 3 or 4 liters of diluted plasma and prescribed a detailed plan for plasma replacement. There may well be additional factors in the shock mechanism. Sepsis, for example, may be an important element in some patients. Impaired pulmonary ventilation is another.

Full realization of the prevalence and degree of hypovolemia developing after perforation should influence treatment in many ways. Surgery should not be undertaken until adequate correction has been accomplished. The correction should be guided by appreciation of the fact that a normal blood pressure may merely represent vasoconstrictive adaptation to hypovolemia. When the arterial pressure begins to fall in spite of vasoconstriction, the administration of vasoconstrictive drugs will only increase the tissue hypoxia; consequently, such drugs are objectionable. Replacement therapy is inadequate unless satisfactory urine excretion is obtained. As shown by Cope this must amount to at least 20 c.c. of urine excreted per hour. At this rate of excretion, blood volume is adequate to permit release of renal vasoconstriction. Therefore the urine output constitutes an index of blood volume.

DETAILS OF MANAGEMENT

The attainment of optimal results in the treatment of gastroduodenal perforations demand the adoption of a carefully planned program of management. If the present mortality rate is to be lowered importantly, it is necessary to give very close attention to a large number of details. The program should comprise a carefully coordinated plan of concurrent diagnosis and treatment compressing these into a minimum of time. It is not within the scope of this paper to discuss these details. However, we wish to submit the protocol furnished our resident staff as a guide to be used in their work-up and treatment of acute perforations. This protocol somewhat empirically indicates the important details for their consideration in the management of each case. Some of the recommendations are recognizably drawn from the work of authoritative writers to whom space does not permit reference.

PROTOCOL TO BE FOLLOWED UPON ADMISSION OF PATIENT WITH SUSPECTED PEPTIC ULCER PERFORATION

1. Take brief history and do limited physical examination.
2. Give narcotic. Meperidine intravenously is approved. The amount used should be enough to provide a large degree of relief from pain.

3. Insert Levin tube into the stomach so that most proximal opening is 2 inches below the gastric cardia. Aspirate stomach contents. Note amount, character, and acidity of aspirated material. Put patient in lateral decubitus position, left side down, and connect continuous suction to Levin tube.

4. Order urinalysis, hemoglobin, and erythrocyte, white blood cell, and differential count—also, blood urea nitrogen, serum amylase, prothrombin time. Also request blood typing and cross-matching.

5. Insert indwelling urethral catheter, connect to bedside bottle after emptying bladder. On adhesive tape on bottle note time at which collection is started.

6. Begin intravenous repletion therapy. This should include plasma or blood, water, electrolytes, and vitamins. Give plasma first. Use blood if plasma is not available or if patient is anemic. Average patient 6 hours after perforation should receive: 1,000 c.c. 5 per cent dextrose in 0.45 per cent NaCl. Add 500 c.c. plasma "piggy back." Average patient 12 hours after perforation should receive: 2,000 c.c. electrolyte solution and 750 c.c. plasma. Add thiamine, riboflavin, and nicotinic acid mixture with 1 Gm. ascorbic acid. Give 75 mg. vitamin K parenterally.

7. Give large dose of broad-spectrum antibiotic.

8. Complete the history and physical examination including re-examination of the abdomen.

9. Send patient to X-ray Department if general condition permits. Above intravenous therapy is to be carried on during trip. If any clinical evidence of shock has existed, be sure that arterial pressure is near normal in horizontal and sitting position before patient is sent to X-ray Department. Request that films be made in dorsal decubitus and lateral decubitus right-side-up positions. Restart gastric suction as soon as patient returns from the X-ray Department, again with the patient lying on the left side.

10. On return from X-ray Department the diagnosis should be decided upon. If perforation is diagnosed, decide again whether or not shock is present. A near-normal blood pressure, pulse rate less than 100, and urine output of more than 20 c.c. per hour will clearly permit surgery. Surgery may be postponed if re-examination of the abdomen indicates that the perforation probably has sealed. If shock existed on admission further blood or plasma should be procured for administration during surgery. If shock has not been controlled, consultation is required. Tension pneumoperitoneum, if present, may be contributing to shock and should be relieved by abdominal tap. If tap is done, note odor of the gas. If shock is present, give oxygen therapy.

11. During surgery give dextrose in water intravenously; also blood or plasma if indicated by patient's condition. Keep suction on Levin tube. Cool the patient if significant fever is present.

12. Intraoperative day, have blood pressure recorded frequently. Treat any hypotension aggressively. Secure blood volume determination to assist in diagnosis of cause of any such hypotension, if hemoconcentration has been corrected.

13. First postoperative day, give 2,000 c.c. of 5 per cent dextrose in water. Add 2 Gm. KCl to each liter if satisfactory renal function has been established. If perforation produced severe peritoneal injury, give another 500 c.c. of plasma or blood.

14. Remainder of postoperative period, in the absence of a nephropathy, give enough water intravenously to maintain a urine output of 750 c.c., using 5 per cent dextrose in 0.45 per cent NaCl with the addition of 2 Gm. KCl per liter. One thousand cubic centimeters of 10 per cent protein hydrolysate should also be given daily if the patient is malnourished or if septic complications are present. If calories are critically needed, give 600 c.c. intravenous fat daily and use 10 per cent dextrose in the intravenous fluids. If early recovery seems doubtful, substitute Butlers' solution in 5 per cent dextrose for the 5 per cent dextrose in 0.45 per cent saline in order to provide both potassium and phosphorus.

15. On alternate days check serum Na and K. Use these findings as a guide to therapy in conjunction with the clinical findings.

16. Continue the heavy antibiotic therapy until culture and sensitivity reports are available from the peritoneal fluid obtained at surgery. Discontinue on clinical grounds.

17. While any significant infection exists, furnish 500 mg. ascorbic acid daily, additionally thiamine 50 mg., nicotinic acid 25 mg., and riboflavin 2 mg. per day.

DETAILS REGARDING THE OPERATIVE TREATMENT

1. If the patient is in serious condition, infiltrate the abdominal wall and properitoneal tissues with Pontocaine along the line of the incision, to assist the general anesthesia.

2. Whenever simple closure seems at all precarious, a tag of omentum or other locally available fat redundancy should be used to re-inforce the closure. This should be applied as a pedicle graft, suturing only the edges of the fat to the area around the closed perforation. If through-and-through catgut sutures have been used in the closure, the omental graft should be done with special care because of the danger of catgut digestion and resultant reperforation. Never tie the ends of previously placed sutures over a tag of omentum.

3. For temporary gastrostomy, use No. 28 Foley catheter. If this can be brought through omental edge easily, do so. Gastrostomy is usually indicated for patients over 60 years of age and for cases under that age having severe peritoneal injury.

4. If major concern exists regarding security of closure of a duodenal perforation, use a Robinson catheter for gastrostomy and pass the tip beyond the pylorus.

5. Biopsy all gastric perforations if gastrectomy is not done.

6. If peritoneal fluid is abundant, lavage peritoneal cavity with normal saline after closure of the perforation.

7. Determine as accurately as possible whether the ulcer is acute or chronic and whether or not it is sealed. Also determine the size of the perforation.

SUMMARY

The standard method of management of gastroduodenal perforation due to peptic ulcer should be simple closure of the perforation. This method assures positive control of the lesion. The necessary laparotomy largely eliminates diagnostic error. Mortality is rarely due to the method itself. Gastric suction alone will control the perforation in a very high percentage of cases. There is no proof that it does more than demonstrate the frequency of self-sealing. However, a rapid and precise method for the determination of such sealing might eliminate the need for emergency surgery in a large percentage of cases. The great importance of acute duodenal ulcer as a cause of perforation has been established in England. Such ulcers usually do not become chronic. It is imperative that their frequency and natural history be determined in the United States. In selected cases, ulcer-curative surgery can be applied at the time of perforation, with very low mortality. It is justified only when there is adequate evidence of the presence of progressive ulcer disease. The most important consideration in further reduction of mortality is the preoperative care of the individual patient. Hypovolemic shock probably is the most inadequately treated lethal factor.

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Surgical History

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THE HISTORICAL DEVELOPMENT OF METHODS OF HEMOSTASIS

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HEMOSTASIS has been the concern of mankind since the dawn of time. Its history is intimately interwoven with the significant events of all ages. The advent of warfare, gunpowder, printing, and anesthesia[1] has had a profound effect on progress in hemostasis.

Customarily in modern times hemostasis is thought of primarily as within the surgeon's domain. The words of William Halsted are pertinent in this regard[10]: "One of the chief fascinations of surgery is the management of wounded vessels and the avoidance of hemorrhage. The only weapon with which the unconscious patient can immediately retaliate upon the incompetent surgeon is hemorrhage. If he bleeds to death, it may be presumed that the surgeon is to blame, whereas if he dies of infection, or from an unphysiological operative performance, the surgeon's incompetence may not be so evident."

Primitive man realized the dangers of rapid blood loss. When he slew an animal or an enemy he observed that death came quickly after a rapid flow of blood. Perhaps he noted that the injured animal would seek to stop the flow of blood by applying its paw to the wound. Undoubtedly he observed the coagulation of blood after slaying an enemy. In general, hemostasis was achieved by direct compression, tight bandages, and vegetable stypties. Most often attempts at hemostasis were futile and death ensued. Study of aborigines today show no advance over these methods of primitive man.

As the world grew older, men rose up and took it upon themselves to treat the ills of others. Hemostasis was their major problem. Fortunately we have several documents concerning ancient Egyptian medical practice. Egyptian medicine reached its zenith around the year 1600 B.C. Several medical papyri supply us with information; however, the Ebers' Papyrus discovered by Ebers at Luxor in 1873 is most complete. According to this papyrus, the surgeons of that era used stypties widely. These stypties were made of either mineral or vegetable matter and arrested hemorrhage by means of their astringent qualities. They used such substances locally as lead

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sulfate, antimony, and copper sulfate. It is noteworthy that several thousand years later, during the Middle Ages, the use of copper sulfate became popular in Europe as a local hemostatic agent and was known as the "hemostatic button."

Bleeding was controlled in ancient India by elevation, cold, compression, and hot oil. The Chinese, in the era 1000 B.C., used tight bandaging and styptics.

During the Hippocratic age of Greece, it was believed that blood was the chief material of which organs were built. Blood was thought to be produced in the liver. Operative procedures were largely those that could be performed with minimal hemostasis. Ligation of vessels was unknown and amputation was done only below the line of demarcation through the gangrenous zone, where it was observed that bleeding did not occur. Accidental hemorrhage was controlled by styptics, elevation, compression, and bandage. The hot cautery was occasionally used.

The Greek physician and anatomist, Herophilus (335 to 280 B.C.), distinguished veins from arteries. He said that veins were weak and thin walled, containing only blood, whereas arteries were thick walled, containing air "pneuma" and blood. He founded the doctrine of the pulse and counted the pulse rate with a water clock.

As the Greek nation declined, its medicine and ideas migrated to Rome. It is strange indeed to realize that few of the great physicians of Rome were actually Romans. Among Romans of high estate, medicine and particularly surgery was looked upon as vulgar, cruel, and mercenary. The renowned Celsus was probably not a physician but a compiler and encyclopedist. Most of our knowledge of hemostasis and surgical practice in the first and second centuries A.D. come from the writings of Celsus.[8] Celsus himself advocated amputation at the line of demarcation, whereas Archigenes (A.D. 48-117) for the first time advocated amputating for tumors and gangrene above the line of demarcation, first ligating the vessels. Heliodorus, in this same period, gave the first account of the ligation and torsion of blood vessels in operating for hernia but not for amputation. He still amputated below the line of demarcation for fear of uncontrollable hemorrhage. The art of surgical instrument-making flourished during this period. Rufus of Ephesus, at the end of the first century, observed that an artery severed through part of its circumference would continue to bleed but an artery that was completely severed would contract and after a short while bleeding would cease. This lesson unfortunately has had to be relearned frequently since then. This esteemed surgeon arrested hemorrhage by styptics, cold, compression, ligation, and torsion. Antyllus, it is said, treated small peripheral traumatic aneurysms by ligating both ends and puncturing the center. He advised against this practice in large aneurysms.

Galen, the leading physician of Rome, advised that when blood was discharged from a superficial vessel, the finger be placed on the orifice of the vessel and that after a while a thrombus would form and the bleeding stop.

However, if the vessel were deeper it should be ascertained whether it was a vein or artery. If it was a vein, a styptic or pressure would suffice; however, for an artery he advised transection or ligation of it with linen. He even mentioned a shop on the Via Sacra in Rome where a good quality linen could be purchased for this purpose.

Following Galen and the decline of the Roman Empire, the long dark night for European surgery began. Surgical progress ceased; ignorance and inertia prevailed. The knowledge of the ancients was forgotten.

All was not lost, however, as a result of the rise of a new culture and a thirst for knowledge in the East. We find Arabian medicine at its peak during the seventh, eight, and ninth centuries. Bagdad was the center of learning and medicine flourished. The chief importance of Arabic medicine lies not in its originality or accomplishments, but in the fact that in the long interval that separated the decay of Greco-Roman learning from the Renaissance, it represented the most faithful tradition of ancient wisdom and was the principal source of European knowledge and ideas.[9, 15] The most authentic edition of Galen's works available today is the Arabic translation.

Fig. 1.—Varied shaped cauteries used in the fourteenth century.

The great Arabian teachers were Rhazes, Albucasis, and Avicenna. Among these men surgery was considered an inferior branch of medicine and the hot cautery replaced the knife. In the compendium on surgery, *Altasrif*, written by Albucasis (A.D. 936 to 1013) the cautery was strongly advised for hemostasis.[2] Varied shaped gold and iron cauteries were advocated. According to Albucasis, the assistant placed his finger on the orifice of the bleeding vessel while the surgeon prepared and inserted the properly shaped hot cautery. The Arabic fixation on the cautery left its mark since Ambroise Paré, who used the cautery extensively in his early days, quoted Avicenna and Albucasis as his authorities.

As Arabic surgery declined, European surgery slowly awakened from its long sleep. Hugo of Lucca and his son Theodoric (A.D. 1205 to 1298) practiced surgery in Bologna. They were original thinkers, teachers, and active surgeons.[14] Arterial and venous bleeding were carefully differentiated. The signs and symptoms of shock and its poor prognosis were recognized. They advocated many methods of hemostasis, including the primary suture of wounds; however, they stressed digital compression until clotting occurred followed by firm bandaging. Transection and ligation of arteries was also practiced by Theodoric reserving cautery only for wounds where putrefaction was present. The surgeons of this period quoted Galen extensively in all matters. It was Henri de Mondeville who said, "God did not exhaust all His creative power when He made Galen."

Guy de Chauliac and Henri de Mondeville in the early fourteenth century used stypties, acupressure, torsion, and ligation of isolated vessels by means of a sliding noose ligature. They began to study anatomy with great intensity. Guy de Chauliac said, "The surgeon ignorant of anatomy carves the human body as the sculptor carves wood."

The fifteenth century brought many changes. The use of gunpowder became widespread and the art of printing developed rapidly. Surgical books rolled off the presses with vital new information on the treatment of gunshot wounds. Jerome of Brunswick (Hieronymus Brunschwig), an Alsatian army surgeon, wrote a textbook of surgery in 1497. His treatment of gunshot wounds is the first detailed account in medical literature.[3] Although the use of ligatures in modern times is usually attributed to Paré, Jerome, preceding Paré, described its use accurately and stated that when feasible, it is the best way of combating hemorrhage. John de Vigo and later Ambroise Paré extended the use of the ligature.

The life of Paré and his radical departure from the classical treatment of gunshot wounds are well known. In 1552 Paré again startled the surgical world. He amputated a leg above the line of demarcation as Archigenes had done and he ligated the vessels with linen, leaving the ends long.[13] When describing this case he wrote, "I dressed him and God healed him." Paré ligated vessels by grasping them with the "Bec de Corbin," the ancestor of the modern hemostat. Previously vessels were grasped with hooks, tenaculum, or by the assistant's fingers. The ligature was gradually accepted by most surgeons; however, Fallopius and Hildanus refrained from using the ligature in amputations. In the seventeenth century it was generally taught: "Ligate if the wound is clean and cauterize if purulent or dirty."

Ligation of vessels, when finally accepted by the surgical profession, was a step forward in hemostasis; however, in extensive wartime injuries to extremities there was often not the time, equipment, or skill available to achieve hemostasis. The tourniquet slowly developed starting in antiquity as a tight bandage. It was Morel, the military surgeon on the battlefield in 1674, who first introduced a stick into the bandage and twisted it until the arterial flow

stopped. The screw tourniquet came into use shortly thereafer. Were it not for the tourniquet and the confidence it gave to surgeons, the time-consuming ligature would not have gained popularity.

In 1873 Freidrich Von Esmarch, a student of Langenbeck, introduced his elastic tourniquet bandage for first aid use on the battlefield. It had previously been thought that such compression would irreversibly injure the vessels. Following Esmarch, surgeons operated electively on extremities in a dry, bloodless field.

Fig. 2.—Screw tourniquet, sixteenth century (after Petit).

As the age of scientific medicine approached, a more thorough understanding of hemostasis came about. Petit, and later Jones, described the formation of a coagulum above the ligature or in a transected vessel. They taught that coagulation was essential for hemostasis. Jones noted that injury to the intima of the artery by the ligature caused a clot to form. With this new knowledge some surgeons began to cut their ligatures short and leave them buried. Due to the nonabsorbable nature of the ligatures plus the ever-present contamination, the wounds suppurated, ejected the buried material, and fatal secondary hemorrhage occurred. In 1806 Phillip Syng Physick, the Philadelphia surgeon trained by John Hunter, introduced absorbable ligatures made of buckskin and parchment. He experimented with these ligatures in animals proving that they were absorbable. Another American, Horatio Jameson, continued the work of Physick and in 1824 introduced ligatures of chamois and kid. The technical advances in suture material came rapidly after the introduction of ether anesthesia and antiseptic surgery.

Sir Joseph Lister had a consuming interest in absorbable suture materials.[12] According to Lister, the ideal suture should be sterile, pliable, unreactive, strong, and absorb when its function has ceased. Although catgut had been known to the Homeric Greeks, its use prior to the investigations of Lister had been very limited. Lister noted that plain catgut, which had

not been treated in any way, became extremely soft and pulpy when exposed to bovine serum. Over the course of several years he used carbolic acid, tannic acid, and finally chromic acid to prepare the catgut for surgical use. He found that chromacizing catgut resulted in a longer-lasting safer suture material. In the early days of the use of catgut, tetanus, anthrax, and gas gangrene resulting from its use were common. As late as 1931, Meleny reported several cases of fatal gas gangrene and tetanus.

With the passage of years and the perfection of the aseptic technique, nonabsorbable sutures again became popular. The classic work of Halsted in 1913 described his careful silk technique and its successful use.[7]

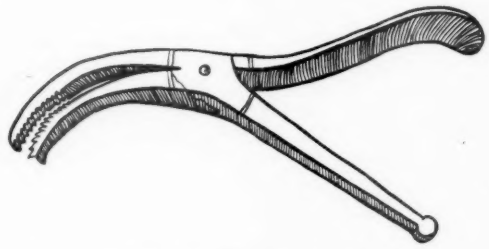

Fig. 3.—"Bec de Corbin" (after Paré).

The hemostat probably came into being in Hippocratic times as a dental tooth extractor. Later the Roman and Arab surgeons used these instruments for foreign bodies. Paré and Scultetus developed the Bec de Corbin and used them for grasping vessels. In the nineteenth century when it was thought imperative that the vessels be isolated first, finer instruments were developed. Von Graefe, in 1829, developed a lock to hold the instrument closed. In 1839, Liston of London began to use the hemostat. In 1800 Phillip Physick invented a hemostat and a needle holder. Pean in 1867[4] and Spencer Wells in 1872 developed hemostats with catches. The status of the hemostat in this country has been described by Halsted. "On my return from Germany in 1881, I was impressed with the fact that our surgeons were greatly handicapped in most of their operations by lack of proper instruments, particularly of artery clamps. They were insufficient in number and faulty of design. The tenaculum was in common use. One text of surgery has a picture of a tenaculum applied to a vessel and the handle held in the mouth of the operator for the want of an assistant. Rarely have I seen in this country prior to 1879 more than one artery clamp at a time left hanging in the wound." Halsted himself finally developed the modern fine-nosed hemostat which is used today.

There have been many approaches to the problem of hemostasis employing the technicologic advances of the past century. In 1892, Horsley[11] described an antiseptic hemostatic bone wax. Subsequently, Harvey Cushing[5] used silver clips to obtain hemostasis in the newly-developed neurosurgical science. He also employed electricity in the form of the electric cautery as an aid in hemostasis.[6]

In recent years the surgical armamentarium has continued to grow, based upon the knowledge of the physiologic and biochemical properties of blood

and its coagulation. A surgeon's method of achieving hemostasis is still the highest criterion of his skill. In an ever-changing world, this remains constant.

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Book Reviews

CONDUCTED BY J. GARROTT ALLEN, M.D.

The Compleat Pediatrician. W. C. Davison and Jeana Davison Levinthal. Ed. 7. Durham, N. C., 1957, Duke University Press. Pp. 257. $4.50.

This is an extensively revised edition of a handbook type of pediatric reference that has enjoyed considerable popularity through six preceding editions. It is written in a manner that achieves the maximum density of facts. Its further breadth of coverage, without increased bulk of book, is attained through the use of extensive (and easily followed) cross-indexing.

Information covering the main aspects of clinical pediatrics is included in this book which is almost small enough to fit into a large pocket.

The chapters dealing with descriptions of diseases make up the largest part of the book. The subject matter is organized according to organ systems and much of the material can be easily located without reference to the index. The disease descriptions are essentially listings of pertinent historical facts, signs, symptoms, and laboratory tests; treatment and prognosis are also covered. This information is so presented that it may helpfully "jog the memory" of one somewhat familiar with the material or indicate avenues for further inquiry. However, one who has no previous acquaintance with the subject at hand might well be more confused than helped.

In the section dealing with laboratory and other procedures, there is presented a brief description of the method and the interpretation of the results of the procedures that one would ordinarily expect to need in dealing with children.

The chapters on well child care and general measures of treatment set forth factual information about such things as criteria of normal physical and neuromuscular development, nutritional requirements, and the many other bits of data that the physician dealing with children would sometimes need. The section on drugs and prescriptions is useful in the same way.

This book is a convenient source of reasonably accurate factual material about pediatric problems.

—Marc O. Beem

Cryptorchism. Charles W. Charney and William Wolgin. New York, 1957, Paul B. Hoeber, Inc. Pp. 140. $5.85.

In handling the confused subject of cryptorchism, the authors have written a lucid and readable book. It is pointed out that two main schools of thought exist regarding the spermatogenic deficiency of the cryptorchid testis—congenital or environmental defects or both. Largely due to this difference of interpretation, opinions vary as to proper methods of treatment. The authors' expressed intention is "to compile the published data, analyze further the clinico-pathological aspects of cryptorchism and the need for correcting the anomaly, and ultimately to arrive at conclusions which will serve to draw the two schools of thought together." This expressed intention of the authors is admirably accomplished.

The authors' conclusions on the histologic pattern of undescended testis are based upon 45 bilateral testicular biopsies in 30 patients, taken at the time of and following

orchiopexy. They conclude that it is only after the age of 10 years that degenerative changes begin in the testis which, because of mechanical factors, has failed to descend. They performed 73 testicular biopsies on infertile adults who had been subjected to orchiopexy before puberty by other surgeons. In *not one case* did they find normal spermatogenesis. Since improvement of spermatogenesis is the chief purpose for treating cryptorchism and since uncomplicated *unilateral* cryptorchism is usually associated with the development of normal fertility, the authors do not advise orchiopexy for boys with this condition. Newer surgical methods are alleged to produce better results. However, the authors advise orchiopexy in *bilateral* cryptorchid boys before the age of ten.

Intelligently discussed in relation to cryptorchism are subjects of spontaneous descent, testicular malignancy, hormonal treatment, and removal of the affected testis. Twenty-eight photomicrographs of testicular biopsies add greatly to the value of this carefully written book. Anyone interested in this subject should find this monograph to be a useful guide.

—John L. Sommer

Calendar of Surgical Meetings

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 5-8, 1958, Royal York Hotel, Toronto, Ontario, Canada. Secretary, Dr. Robert McLaurin, University of Cincinnati, Cincinnati, Ohio.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 2-4, 1958, The Drake Hotel, Chicago, Ill. Acting Secretary, Dr. James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 20-21, 1958, Biltmore Hotel, New York City, N. Y. Secretary, Dr. Scott Hill. Subject, cancer of the colon and rectum.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 6-10, 1958, The Conrad Hilton, Chicago, Ill. Secretary, Dr. Michael L. Mason, 40 E. Erie St., Chicago, Ill.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* Dec. 2-5, 1958, Leamington Hotel, Minneapolis, Minn. Deadline for submission of abstracts, Aug. 1, 1958. Secretary, Council on Scientific Assembly, Dr. Thomas G. Hull, 535 North Dearborn St., Chicago 10, Ill.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Sept. 26 and 27, 1958, Poland Spring House, Poland Springs, Maine. Deadline for submission of papers, June 20, 1958. Secretary, Dr. J. Gordon Scannell, The Warren Bldg., 275 Charles St., Boston 14, Mass.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 12-14, 1959, Denver, Colo. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 9-11, 1958, Boca Raton Hotel and Club, Boca Raton, Fla. Attendance by invitation of membership only. Secretary, Dr. George G. Finney, 2947 St. Paul St., Baltimore 18, Md.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.